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CONTENTS OF PREVIOUS NUMBER

AUGUST 1948. NUMBER 2

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VOLUME 60 SEPTEMBER 1948 NUMBER 3

CHANGES IN BRAIN STRUCTURE AND MEMORY AFTER INTERMITTENT EXPOSURE TO SIMULATED ALTITUDE OF 30,000 FEET

A. V. JENSEN, Ph.D.
CHAPEL HILL, N. C.

R. F. BECKER, Ph.D.
SEATTLE
AND
W. F. WINDLE, Ph.D., Sc.D.
PHILADELPHIA

WE ARE interested in the effects of asphyxiation on the nervous system and have described changes taking place in the brain after resuscitation of newborn animals.[1] More recently, we undertook to determine effects on nerve cells of intermittently subjecting adult animals to reduced pressures of oxygen, reporting results of experiments at a simulated altitude of 23,000 feet (7,700 meters; 307 mm. of mercury).[2] It was found that guinea pigs living at the lowered barometric pressure in a chamber, six hours a day and six days a week for periods totaling as much as five hundred hours, exhibited no significant symptoms, nor did the brains show appreciable histopathologic changes with carefully controlled technics. One could not observe any cumulative effect of the day by day exposure. The study demonstrated that greater degrees of anoxia would have to be used to bring about significant structural changes in the nervous system. The present communication is concerned with two other groups of experiments, in which a simulated altitude of 30,000 feet (10,000 meters; 225 mm. of mercury) was used. In addition to making the experimental conditions severer, we have extended the investigation to include a study of the effects on memory.

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

From the Institute of Neurology and the Department of Anatomy, Northwestern University Medical School, and the Department of Anatomy, University of Washington Medical Department.

1. Windle, W. F.; Becker, R. F., and Weil, A.: Alterations in Brain Structure After Asphyxiation at Birth, J. Neuropath. & Exper. Neurol. **3**:224 (July) 1944.

2. Windle, W. F., and Jensen, A. F.: A Study of the Brain After Intermittent Exposure to a Simulated Altitude of 23,000 Feet, J. Aviation Med. **17**:70 (Feb.) 1946.

Although many clinical and experimental studies of the effect of asphyxiation, anoxia, hypoglycemia, arrest of the cereberal circulation and related conditions on the nervous system have been reported,[3] few investigators have dealt with the problem of intermittent exposure to reduced pressures of oxygen. Armstrong and Heim [4] subjected rabbits to conditions simulating an altitude of 18,000 feet (6,000 meters; 370 mm. of mercury) for four hours daily over a period of five weeks. Although they reported venous congestion of the brain, edema around the periphery of the medulla oblongata and small subcapsular hemorrhages in the spinal cord, they carried out no histologic studies on the central nervous system. Oster and Toman [5] published a brief report of experiments with cats. In 5 animals receiving twelve to twenty-one daily exposures to atmospheres of low oxygen concentration, they observed blindness, deafness, cachexia, anorexia and general depression of reflexes. The oxygen tensions at which changes occurred were not specificially stated. Sections of the brain revealed chromatolyzed cells in the cerebral cortex, as well as damage to the lateral geniculate bodies. Tannenberg [6] subjected rabbits repeatedly to severe anoxic shock. Although he did not indicate what histologic technics were used, he described damage to the cerebral cortex, cerebellum, hippocampus, medulla oblongata and spinal cord. He indicated that the results were variable. A group of investigators in Germany, whose reports were reviewed by Büchner [7] and later by Altmann and Schubothe,[8] described changes in the structure of the central nervous system after intermittent, as well as continuous, exposures to conditions simulating high altitudes. One of this group of investigators, Dellaporta,[9] stated that the changes in the central nervous system were

3. Hoff, E. C.; Grenell, R. S., and Fulton, J. F.: Histopathology of the Central Nervous System After Exposure to High Altitudes, Hypoglycemia and Other Conditions Associated with Central Anoxia, Medicine **24**:161 (May) 1945.

4. Armstrong, H. G., and Heim, J. W.: The Effect of Repeated Daily Exposures to Anoxemia, J. Aviation Med. **9**:92 (June) 1938.

5. Oster, R. H., and Toman, J. E. P.: Chronic Hypoxia in the Cat, Federation Proc. **2**:37 (March 16) 1943.

6. Tannenberg, J.: Comparative Experimental Studies on Symptomatology and Anatomical Changes Produced by Anoxia and Insulin Shock, Proc. Soc. Exper. Biol. & Med. **40**:94 (Jan.) 1939.

7. Buchner, F.: Ueber experimentelle Höhenpathologie (vom Standpunkt des Pathologen), Luftfahrtmed. **5**:1, 1940.

8. Altmann, H. W., and Schubothe, H.: Funktionelle und organische Schädigungen des Zentralnervensystems der Katze im Unterdruckexperiment, Beitr. z. path. Anat. u. z. allg. Path. **107**:3, 1942.

9. Dellaporta, A. N.: Die Veränderungen des Zentralnervensystems nach Luftverdünnung und nach Hunger, Beitr. z. path. Anat. u. z. allg. Path. **102**:268, 1939.

unrelated to duration of exposure to low partial pressures of oxygen but depended on starvation accompanying the exposures to anoxia.

The most recent study of the brain after intermittent anoxemia is that of Morrison,[10] who used dogs as subjects and employed atmospheres containing reduced amounts of oxygen. The oxygen in the blood was estimated to be 4.5 to 13 volumes per cent. He also examined the brains of monkeys which had been subjected to reduced barometric pressures simulating altitudes of 30,000 feet. Widespread structural changes were described, but not all were related entirely to the experimental conditions, for they appeared in less pronounced form in the controls.

From a review of the literature on effects of intermittent exposure to lowered oxygen tensions, the only conclusion to be reached is that a variable amount of damage to the central nervous system results if the amount of available oxygen is low. It is not certain that all the changes described have been due to the anoxia itself. The histopathologic picture has not been clearly portrayed, and the histologic technics have been inadequately controlled. No information is available concerning changes in memory in animals as the result of intermittent exposure to high altitudes.

MATERIAL AND METHODS

Young adult male guinea pigs were used in the present study. They were maintained under laboratory conditions for several weeks prior to beginning the experiments. During that time, and throughout the experiments, they were fed the Rockland Farms balanced diet in the form of pellets and were given an abundance of water. The animals were kept on wire and had access to salt blocks. They were weighed twice a week.

A decompression chamber with a capacity of 1,650 liters was used. The animals were placed in cages which could be kept under observation through glass windows in portholes. The temperature was kept within the range of 21 to 23 C. Carbon dioxide was not a factor, for the capacity of the evacuation pump was great enough that fresh air was drawn through the tank constantly.

In the principal experiment, 15 experimental animals and 9 controls were used. The experimental animals were subjected to decompression for six hours a day six days a week at an atmosphere pressure of 225 mm. of mercury, the equivalent of an altitude of 30,000 feet. The pressure in the tank was reduced gradually, from twenty-eight to forty-four minutes (average thirty-five minutes) being required for ascent and twenty-six to forty-four minutes (average thirty-three minutes) for descent. The control animals were placed in cages, and food was withheld from them during the period in which the experimental animals were at altitude, and during which time they failed to take food. Throughout the study all animals were observed frequently for behavioral changes.

Seven experimental animals from a supplemental experiment were used for the pathologic study, but these were not given memory tests. Three of them received a total exposure of one hundred hours at a simulated altitude of 30,000 feet; 4 were subjected to 23,000 feet for one hundred hours and then to

10. Morrison, L. R.: Histopathologic Effect of Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **55**:1 (Jan.) 1946.

30,000 feet for one hundred hours. Observations on these animals have been mentioned in a preliminary article.[11] Hematologic studies have likewise been described.[12]

Before the series of daily decompressions was begun, the 24 animals of the principal group were trained to run a simple alternation maze (fig. 1) to the point of perfection. The problem was one of circumventing three blind alleys to reach one of two goal boxes. Two of the blinds were wooden barriers; the third was made by closing the entrance of one goal box by a glass panel. Electric grids crossed the floor of the blind alleys, and the adjacent open runways as well. Animals received a shock through the feet whenever they entered a blind alley, but never when traversing an open runway. The shocking switch was controlled at a distance by the observer, who was able to watch the animal's progress in an overhanging mirror. Because of dry and heavily calloused foot pads, a shocking stimulus of 100 to 150 volts seemed only mildly noxious to the animals.

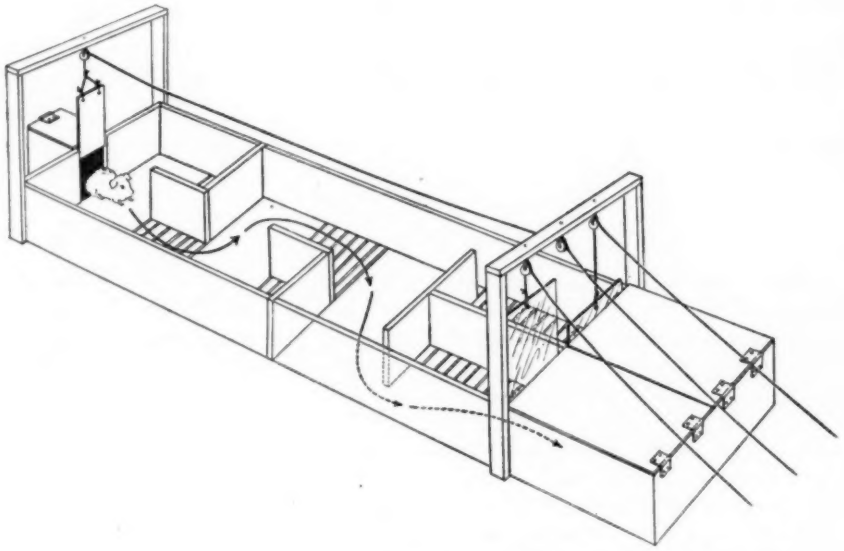

Fig 1.—Diagram of the maze used in testing retention of learning.

Avoidance of punishment and the safety of a darkened goal box provided adequate motivation for learning the maze pattern. Food was also used as a lure, but animals rarely partook of it during the learning process. Since guinea pigs eat continually, starvation for a period prior to testing does not motivate them as effectually as it does the rat and other laboratory animals, which feed once a day on schedule. The problem of learning and motivation in the guinea pig has been discussed elsewhere.[13] Initially, new animals would stall in the

11. Jensen, A. V., and Windle, W. F.: The Brain After Intermittent Exposure to Simulated High Altitude, Arch. Neurol. & Psychiat. **56**:346 (Sept.) 1946.

12. Jensen, A. V., and Alt, H. L.: The Effect of Intermittent Exposure to Simulated High Altitude on Erythropoiesis in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **60**:384 (Dec.) 1945.

13. Becker, R. F.: Some Observations on Learning Ability in the Guinea Pig, Quart. Bull. Northwestern Univ. M. School **20**:318 (Sept.) 1946.

starting pen; but the floor of this pen was also covered with a grid, and, after being shocked out into the maze a few times, the animal ran readily enough. The initial 5 trials were run with wooden barriers removed and with both goal boxes open. After that, initial training was begun with all blind alleys in place.

Learning progressed in three stages. First, the blinds were set so that the animal had to run a zigzag path to the left goal box. The criterion of perfection for this problem was 5 correct and consecutive trials, each executed in less than ten seconds. The animal was then trained to run a similar pattern to the right goal box by the experimenter's merely alternating the position of the blinds. The same criterion of perfection obtained. In the third stage, the blinds were alternated on each trial in a purely chance sequence, the order being the same for each animal. Hence, sometimes the right, and then the left, goal box became the correct avenue of escape from the maze. Under these conditions, the criterion of perfection was 10 correct and consecutive trials.

After an animal had mastered all three stages to perfection, four sets of learning scores were available: (1) a time score, (2) a trial score, (3) a total error score and (4) a repeated error score. Of these, the time score elicited the least valuable comparative data, for some animals normally ran at a faster rate than others who learned as well. These scores were useful only in indicating when a given animal was beginning to learn in terms of progressively reduced running time. Trial and total error scores proved to be the best comparative measures. They indicated objective differences between animals in terms of the total number of trials necessary to meet the criteria of perfection and the total number of errors made in the process. The repeated error scores were a measure of rigidity or perseveration, indicating the number of times an animal repeated the same mistake in a given trial. As one might expect, more repetitions occurred in the early stages of learning than in the later stages.

After initial testing, the animals were turned over to a collaborating investigator (A.V.J.). They had been ranked in order of excellence of performance (table 1); and, except for the number of the animal making the highest score in terms of fewest total trials and errors, no information about the initial maze performance was disclosed to this investigator. Since he was to select at random the control group, which was not to be exposed to simulated altitudes, at least the most superior animal (guinea pig 218) would fall in the experimental group. It so happened by chance that 4 superior and 5 inferior performers were kept as controls. The identity of these controls was not known by the tester (R.F.B.) until the end of the experiment. He did not know even the animals' code numbers, as they appear in table 1.

As the investigation progressed, groups of 4 experimental and 2 control animals were killed, after specific intervals of exposure, for histologic study of the brains. Experimental groups were selected on the basis of physical condition only, weaker animals (with loss of weight and behavior during exposure as criteria) being killed first. They were matched with controls selected at random. Prior to being killed, each group was retested for the chance alteration phase of the problem. Performance on the retest was a measure of retention or memory.

After one hundred hours of exposure all animals were retested. After one hundred and fifty hours the first group, of 6 guinea pigs, had their second retest and were killed. After two hundred hours the remaining animals were given a second retest. Six of this group were then killed. These 6 animals had been selected to be killed prior to knowledge of performance on the second test, and their identity was not known by the test administrator. At the end of

two hundred and fifty hours the remaining animals (4 experimental and 5 control pigs) had a third retest and were killed.

The animals were killed twenty-four to forty-eight hours after the last exposure to low barometric pressure. Retention was tested within this period. Each animal was then anesthetized with "pentobarbital sodium" intraperitoneally and perfused at a pressure of 70 mm. of mercury through the aorta with isotonic sodium chloride solution U. S. P. containing acacia, to wash the blood out of the circulation; this was followed with a mixture of solution of formaldehyde,

TABLE 1.—*Retention in Terms of Relearning in Animals After One Hundred Hours of Anoxia*

Superior Group					Inferior Group				
Animal Number	Rank at Initial Learning	Trials	Errors	Repeated Errors	Animal Number	Rank at Initial Learning	Trials	Errors	Repeated Errors
218	1	0	0	0	204	13	11	32	7
201	2	..	(Dead)	..	205	14	10	16	6
138*	3	0	0	0	214	15	0	0	0
207	4	15	12	1	135*	16	19	21	1
202	5	3	4	0	211	17	0	0	0
137*	6	9	7	1	133*	18	10	4	0
131*	7	14	21	1	215	19	14	9	2
210	8	0	0	0	136*	20	15	17	5
130*	9	0	0	0	134*	21	13	10	1
209	10	5	4	0	203	22	28	32	7
216	11	0	0	0	132*	23	0	0	0
217†	12	12	10	0	208	24	..	(Dead)	..
Total score.....		58	58	3	Total score.....		120	132	29
Average score.....		5.3	5.3	0.27	Average score.....		10.9	12.8	2.6
C. Averages for Entire Group									
Control total score....		80	80	9	Experimental total score.....		98	119	23
Control average score.		8.9	8.9	1	Experimental average score.....		7.5	9.2	1.8

* Controls (selected originally at random, without knowledge of performance rank).
† Animal eliminated later in experiment.

sodium chloride and acacia to fix all the tissues of the body in situ.[14] These mixtures have been considered elsewhere[15]; with their use, the usual swelling, shrinkage or distortion of neurons, seen in material fixed by immersion in solutions of formaldehyde, was avoided. The brain was placed in the fixing fluid, where it remained for four to five days; it was then embedded in nitrocellulose of low viscosity and sectioned serially at 40 microns. Every tenth section was stained by the technic using a buffered solution of thionine.[16] Alternate tenth sections of the brains of 10 experimental and 3 control animals were also stained by the Weil method for the study of myelin components of nerve fibers. Sections from experimental animals were stained at the same p_H, in fact, in the same dish, with sections from the control animals. Silver stains for axis-cylinders were not used because the study of the Nissl and Weil preparations revealed no need for them. Special glia stains were not employed; with the buffered thionine technic neuroglia were stained adequately for present purposes.

14. In most instances, solution of formaldehyde U. S. P. (3:4) was used in quantities equal to 20 per cent of the animal's body weight.

15. Koenig, H.; Groat, R. A., and Windle, W. F.: A Physiological Approach to Perfusion-Fixation of Tissues with Formalin, Stain Technol. **20**:13 (Jan.) 1945.

16. Windle, W. F.; Rhines, R., and Rankin, J.: A Nissl Method Using Buffered Solutions of Thionin, Stain Technol. **18**:77 (Jan.) 1943.

RESULTS

The behavior of the animals in the decompression chamber at a simulated altitude of 30,000 feet (pressure of 225 mm. of mercury) was similar to that observed previously in animals at 23,000 feet (307 mm. of mercury).[2] Beyond the 18,000 foot (6,000 meter) level (379 mm. of mercury) activity of the animals diminished. At full altitude, rapid bodily movements were rarely seen; when they occurred, they were usually followed immediately by collapse of the animal. The animal would fall on its side and lie there, apparently unconscious, one-half to two minutes, whereupon it would gradually right itself and remain quiet. Collapse occurred in some animals without appreciable exertion. The characteristic position of an animal during exposure was a motionless huddle with hairs erect.

Two animals died of unknown cause in the chamber, 1 during the first exposure and 1 during the third exposure. On one occasion, an animal (210) was observed to maintain its head tilted sharply downward and to one side during recompression, a position suggestive of involvement of the inner ear. The rate of recompression was accordingly reduced; and before normal level was reached the animal was behaving normally. Another animal (211) was discovered in a lethargic condition after recompression. The following morning, it appeared to be well and did not subsequently show abnormalities of behavior. A third animal (217) was eliminated from the experiment after two hundred and twenty-six hours of decompression because it showed symptoms of infection of the respiratory tract and might have menaced the health of the other animals.

Six of the experimental animals were observed to be in a temporary state of collapse during various periods in the chamber. One of these animals exhibited this state three times; 4 animals, twice, and 1 animal, once. The value of these observations is uncertain; animals may have been briefly unconscious at other times unobserved. On no occassion were the 2 animals which died in the chamber observed to be in such a state.

In the experiment in which animals were subjected to decompression at 23,000 feet for one hundred hours before being carried to 30,000 feet, less distress was encountered than in the groups not so acclimatized. In this series, 1 animal was eliminated because of infection of the respiratory tract, and 1 animal (81) exhibited transient signs of vestibular involvement.

The control animals all gained weight steadily. The weights of the experimental animals remained approximately unchanged up to an exposure for one hundred and fifty hours, when a few began to show decrease. Animals which were losing weight were killed first. At the conclusion of the experiment, the remaining experimental animals (the

two hundred and fifty hour group) weighed about 100 Gm. less than the controls. All animals were killed before loss of weight became severe enough to impair the usual activities of eating and running about.

EFFECT ON MEMORY

Retention After One Hundred Hours of Exposure.—In column 2 of table 1 the animals are arranged in decreasing order of performance at the time of initial learning. Hence, animals 1 to 12 constituted the superior 50 per cent of the group; they learned in fewer trials and made fewer errors than did animals 13 to 24. Table 1 particularly illustrates the amount of retentive loss in all animals after one hundred hours in the decompression chamber, i. e., after a twenty-four day interval since initial learning. Retentive loss is expressed in terms of retraining necessary at the time of retest. For example, a retest score of 15-12-1 means

TABLE 2.—*Retention in Terms of Relearning in Animals After One Hundred and Fifty Hours of Anoxia*

Animal Number	Rank at Initial Learning	Retention at 100 Hours			Retention at 150 Hours		
		Trials	Errors	Repeats	Trials	Errors	Repeats
Experimental Group							
218	1	0	0	0	30	17	2
202	5	3	4	0	21	9	1
211	17	0	0	0	40*	21	5
215	19	14	9	2	30	12	6
Control Group							
135	16	19	21	1	0	0	0
136	20	15	17	5	0	0	0

* Animal was still making errors after the fortieth trial; relearning was incomplete.

that an animal required 15 trials of relearning before it could run 10 consecutive trials without error; it made 12 errors in the relearning process, and it repeated 1 of these in the same blind alley in the course of a given trial. A score of 0-0-0 indicated perfect retention; i. e., the animal ran 10 trials directly without error. It is clear that animals which were superior at initial learning required, as a group, significantly fewer retraining trials, made fewer errors and perseverated less at the one hundred hour retest than did the initially poor group. On the other hand, there was no significant difference at this time in retest performance between all the controls, as a group, and all the experimental animals. As yet, none of the animals had shown any symptoms of physical or mental deterioration.

Retention After One Hundred and Fifty Hours of Exposure.—Four experimental animals were observed to be more acutely affected by exposure to low oxygen tension than the others at the end of one hundred and fifty hours. They were given a second retest, along with 2 controls selected at random. Table 2 illustrates a complete reversal in

maze performance in this group between the one hundredth and the one hundred and fiftieth retest. By chance, 2 experimental animals were from the group of initially superior learners and 2 were from the group of inferior learners; both controls were initially poor learners. On the one hundred hour retest, these controls gave significantly poorer responses than did the 4 experimental animals. Yet at one hundred and fifty hours, only ten days later, all the experimental animals exhibited pronounced retentive loss, while the controls were "letter perfect." The loss in the experimental group was far greater than that shown twenty-four days after initial learning. Among these was animal 218, which had made the best score of any during initial learning. It exhibited perfect retention after one hundred hours, yet at one hundred and fifty hours its retention was at as low a level as that of the poorest performers of the group.

TABLE 3.—*Retention in Terms of Relearning in Animals After Two Hundred Hours of Anoxia*

Animal Number	Rank at Initial Learning	Retention at 100 Hours			Retention at 200 Hours		
		Trials	Errors	Repeats	Trials	Errors	Repeats
Experimental Group							
209	10	5	4	0	8	5	0
216	11	0	0	0	16	13	0
214	15	0	0	0	3	1	0
203	22	28	32	7	8	3	0
Control Group							
138	3	0	0	0	0	0	0
130	9	0	0	0	9	0	0

Retention After Two Hundred Hours of Exposure.—After two hundred hours, the remaining animals received a second retest. Four experimental animals, which showed symptoms of distress in the chamber, and 2 randomly selected controls were killed after the test period. It should be stated here that once out of the decompression chamber the experimental animals could not be distinguished from controls. Again, by chance, 2 of these experimental animals came from the group of superior learners, and 2 from the inferior group (table 3). Both controls happened to be selected from the superior group. From the standpoint of retentive loss, the animals selected to be killed at this time seemed more resistant to the experimental conditions than were those killed at one hundred and fifty hours. Three made poorer scores after two hundred hours than they had at one hundred hours, but only 1 of these animals showed any serious retentive loss. The fact remains that all 4 of the experimental animals needed retraining after two hundred hours, whereas the unexposed (control) animals did not.

From the standpoint of its physical condition in the chamber, animal 203 seemed to react to the effects of anoxia as much as the other 3 experimental animals. However, its performance at two hundred hours was better than that at one hundred hours. While the majority of animals had required relatively little retraining at one hundred hours, this animal had undergone the most extensive retraining program of any. Apparently, the extended training exerted a savings effect which tended to mask a more serious state of deterioration of memory.

Retention After Two Hundred and Fifty Hours of Exposure.—The remaining 4 experimental and 5 control animals had had three retests in all. The first, after one hundred hours, followed initial learning by twenty-four days; the second, after two hundred hours, came twenty-one

TABLE 4.—*Retention in Terms of Relearning in Animals After Two Hundred and Fifty Hours of Anoxia*

Animal No.	Rank at Initial Learning	Retention at 100 Hours			Retention at 200 Hours			Retention at 250 Hours		
		Trials	Errors	Repeats	Trials	Errors	Repeats	Trials	Errors	Repeats
				Experimental Group						
207	4	15	12	1	7	6	1	20*	12	1
210	8	0	0	0	8	5	2	20*	16	1
204	13	11	13	1	0	0	0	20*	14	6
205	14	10	16	6	9	7	1	20*	15	2
Average.....		9	10	2						
				Control Group						
137	6	9	7	1	0	0	0	0	0	0
131	7	14	21	1	0	0	0	0	0	0
133	18	10	4	0	0	0	0	0	0	0
134	21	13	10	1	0	0	0	0	0	0
132	23	0	0	0	0	0	0	0	0	0
Average.....		9	8	0.6						

* Animal was still making errors on the twentieth trial; relearning was incomplete.

days after the first retest, and the third, after two hundred and fifty hours, came twelve days after the second retest. These relearning data are presented in table 4. Again, by chance, half the experimental group represented superior initial learners and half initial inferior learners. Two controls were from the initially superior and 3 from the initially inferior group.

After one hundred hours, there was no difference in retest performance between the control and the experimental animals. After two hundred hours, twenty-one days later, the controls turned in a perfect retention record on the second retest. This was true of only 1 experimental animal, but 2 improved somewhat as a result of the last period of retraining. One experimental animal (210), now showing symptoms of physical distress in the chamber, regressed even more than on the previous test. After two hundred and fifty hours, all experimental

animals began to exhibit signs of distress in the chamber. On the third retest, all were unable to relearn the problem, even after 20 trials. The controls, meanwhile, maintained a perfect record.

STRUCTURAL CHANGES IN THE BRAIN

The results of histologic study of the brains of 19 experimental animals which were prepared, together with those of 7 controls, are summarized in table 5. The most striking pathologic change was focal areas of degeneration in the brain. These appeared in all the specimens subjected to two hundred hours or more of decompression,

TABLE 5.—*Animals Used for Histologic Study and Summary of Alterations in the Brain*

Experimental Animal	Stained with Control Animal	Total Hours at 30,000 Feet	Focal Areas of Degeneration	Shrinkage or Blanching of Neurons	Leukostasis
91	123	100	—	+	—
92	123	100	++*	+	?
93	123	100	—	+	?
202	135	150	—	+	—
211	135	150	+	+	?
215	136	150	—	?	+
218	136	150	++	+	+
81	123	200†	++	?	—
82	123	200†	++	?	+
83	...	200†	++	+	+
84	123	200†	++	?	+
203	130	200	+	+	+
209	130	200	+	+	+
214	138	200	++	+	+
216	138	200	++	+	+
204	134	250	++	+	+
205	131	250	++	+	++
207	131	250	++	+	+++
210	134	250	+	+	+

* This is the only specimen in which focal areas of degeneration occurred elsewhere than in the cerebellum, and the only one in which hemorrhages occurred.
† These 4 animals were subjected to one hundred hours at simulated altitudes of 23,000 feet plus one hundred hours at simulated altitudes of 30,000 feet.

but were found in only 3 of the 7 animals receiving one hundred or one hundred and fifty hours of decompression. With 1 exception, all the focal areas of degeneration were confined to the cerebellum. They rarely extended beyond the confines of the vermis. Figures 2 and 3 illustrate these lesions. Appearance varied with the age of the lesions. In early stages, the granule cells and Purkinje cells of the cerebellum were visible, though in such advanced stages of degeneration that they often appeared as mere shadow forms. In the older lesions, Purkinje and other types of cerebellar neurons entirely disappeared and an extensive proliferation of small blood vessels occurred, as can be observed in figure 3. In all instances, the borders between normal brain tissue and areas of degeneration were sharply defined. Normal Purkinje cells were seen almost to the very edge of the focus of degeneration. Usually,

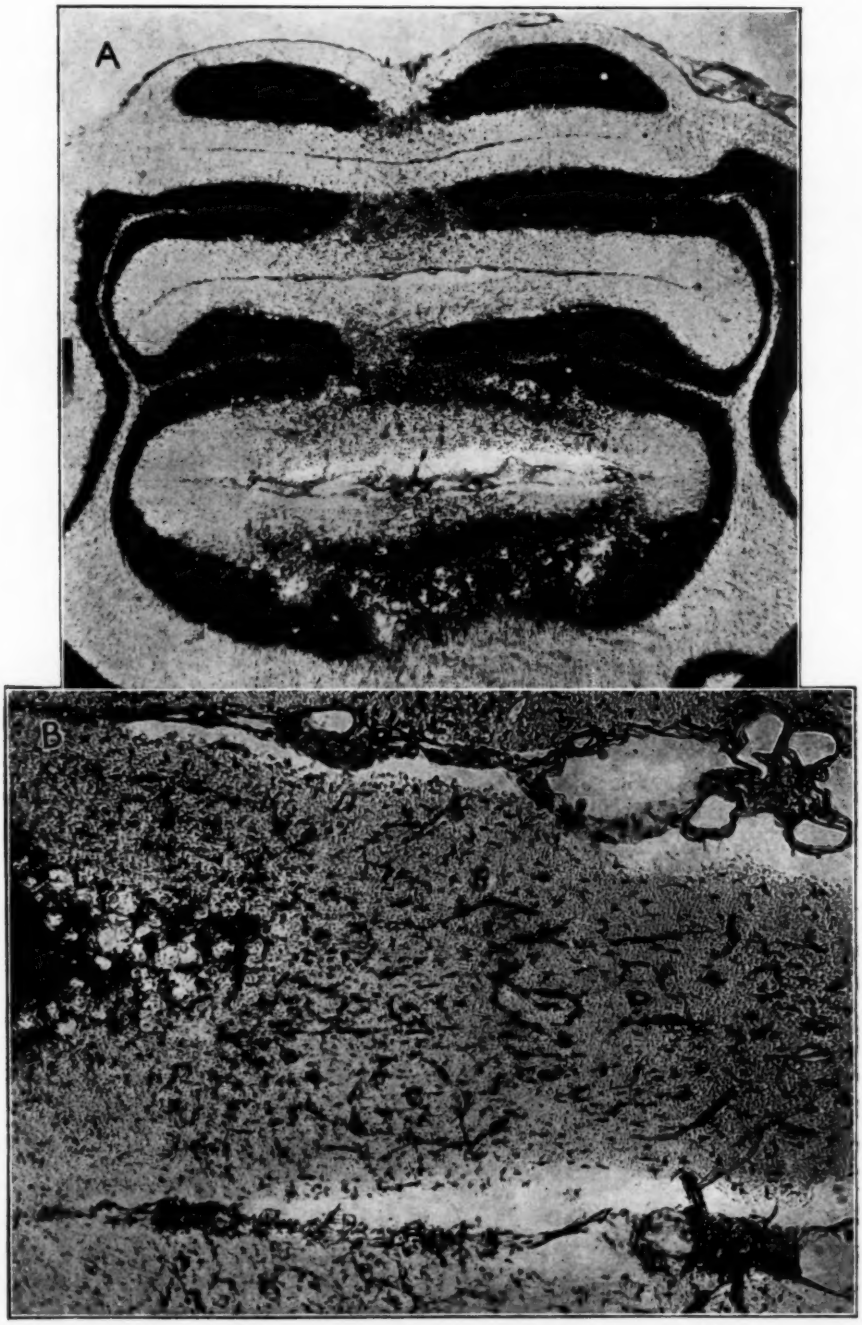

Fig. 2.—*A*, focal areas of degeneration in a section through the vermis of the cerebellum of animal 218, exposed for a total of one hundred and fifty hours at a simulated altitude of 30,000 feet (10,000 meters); thionine stain, × 27.

B, focal area of degeneration from the brain of animal 218, showing vascular proliferation; thionine stain, × 75.

three or four of the nearest Purkinje cells were pyknotic and shrunken, though this was not always observed. Except for these focal areas of degeneration, no histologic changes could be seen in the cerebellum.

Hemorrhages did not occur in the cerebellar foci of degeneration. Only in the case of animal 93, in which foci of degeneration were observed in the cerebral cortex, hippocampus and diencephalon, were paravascular extravasations of the red blood corpuscles seen. These appeared to be recent. They were associated with large areas of beginning degeneration, in which demyelination of the fiber tracts was prominent.

No alteration of the neuroglia of the brain was observed beyond the foci of degeneration. Many small swollen, vacuolated cells, probably transformed microgliocytes (gitter cells), were seen there. No extensive proliferation of astrocytes was encountered.

No widespread degenerative changes were observed in the nervous system. Only by careful comparison of sections from the controls with those from the experimental animals was it possible to ascertain that there had been alteration in neural elements other than those in the definite focal areas of degeneration just described. One could observe no reduction in the number of nerve cells of the principal neuron groups. No thinning of the cerebral cortex could be seen. The hippocampus, usually considered a region readily affected by lack of oxygen, appeared to be entirely normal except in the 1 specimen in which hemorrhages were observed. Only in small, scattered foci throughout various parts of the brain, but notably the cerebral cortex, diencephalon, midbrain and medulla oblongata, was anything observed indicative of a disturbance of the normal structural picture. In such areas, illustrated in figures 4 and 5, shrinkage of nerve cells occurred. This was never very prominent. In fact, without controls, this change might easily have been passed over as nothing more than a slight artefact. In a few foci, there appeared to be impairment of staining of certain neurons, especially the smaller cells. Certainly, without the use of simultaneously stained control material, this slight impairment of stainability would have been overlooked. Myelin sheaths of nerve fibers were unaffected except in the areas of degeneration.

A most striking condition was observed in 2 of the animals which had been subjected to reduced barometric pressure for two hundred and fifty hours. These animals, 205 and 207, exhibited masses of leukocytes in many of the blood vessels of the brain. Such a condition is illustrated in figure 7. All the other animals which had been subjected to two hundred hours or more at the simulated altitude of 30,000 feet exhibited this condition, though in lesser degrees. Six of the remaining 11 animals subjected to less severe experimental conditions likewise showed evidence of this leukostasis.

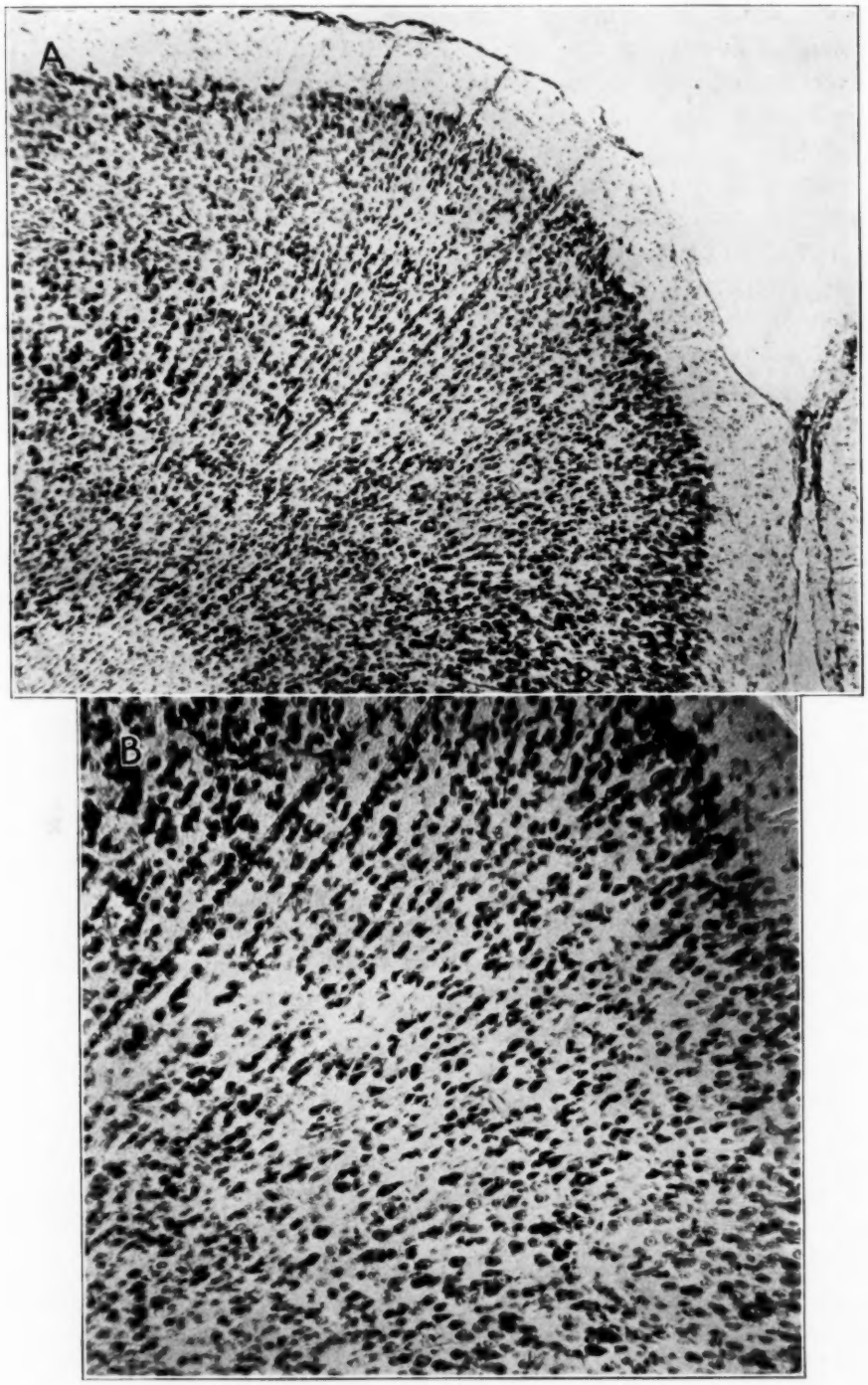

Fig. 3.—*A*, focus of shrinkage of neurons in the cerebral cortex of animal 218, exposed for a total of one hundred and fifty hours at a simulated altitude of 30,000 feet; thionine stain, × 75.

B, higher magnification of a portion of the section shown in *A*; × 125.

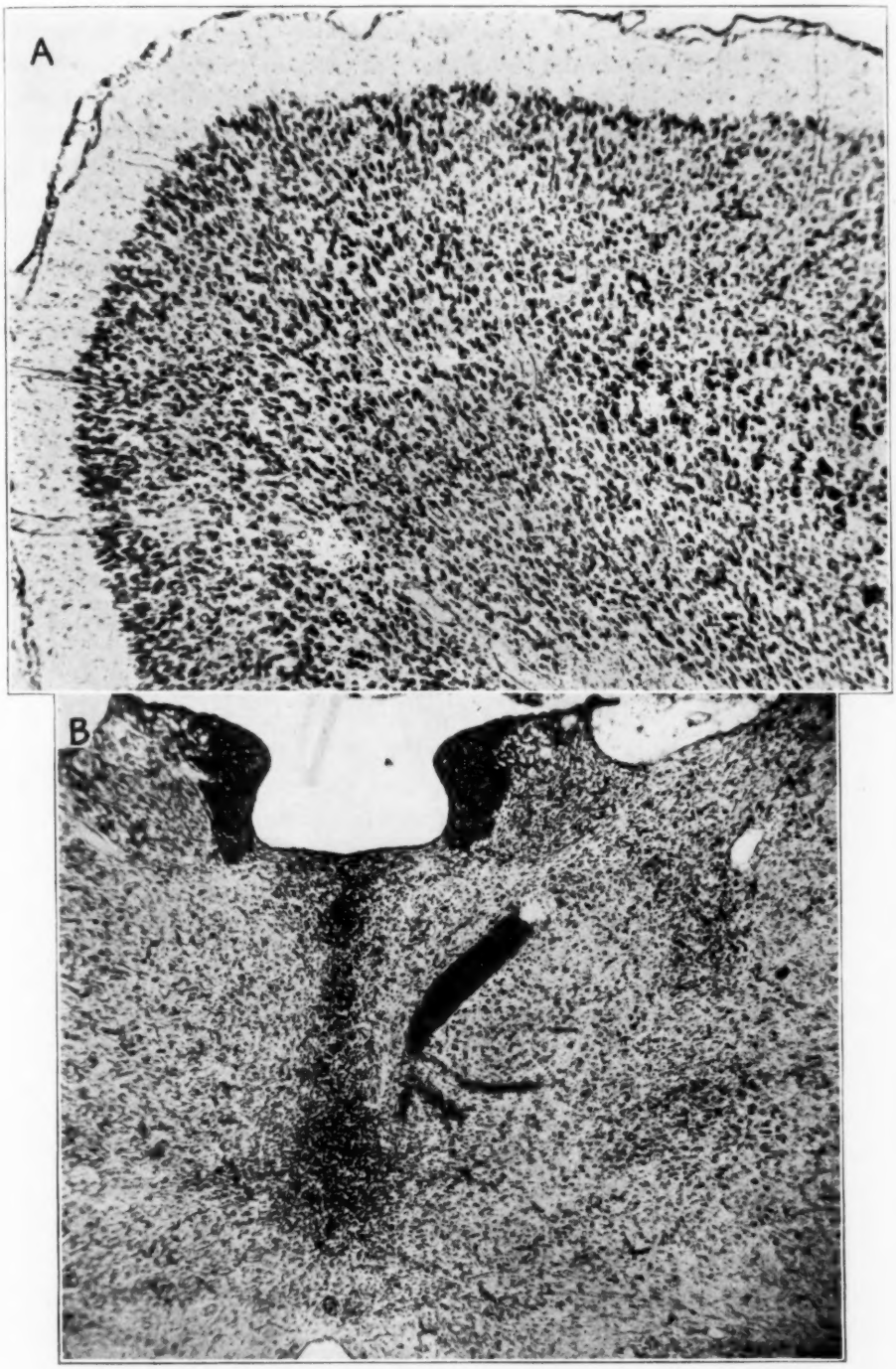

Fig. 4.—*A*, section of the cerebral cortex of control animal 136, stained with the section shown in figure 3 (animal 218), from the corresponding region; × 75.

B, leukostasis present in a section of the diencephalon of animal 207, exposed for a total of two hundred and fifty hours at a simulated altitude of 30,000 feet (10,000 meters). The blood vessels are filled with leukocytes, but there is no degeneration of nerve tissue (see text). Thionine stain, × 33.

In its most conspicuous form, the leukostasis was observed in vessels not only within the brain substance, but also in the meninges. The apparently plugged vessels of the brain were not surrounded by areas of degeneration. Therefore, there could not have been complete vascular occlusion at these sites during life. It should be recalled that the vascular system was perfused while the heart was still beating. As much blood as possible was washed out with saline solution, partly by the action of the beating heart. After this perfusion, the fixing fluid was run in. Had there been a leukostasis, with the leukocytes sticking to vessel walls, it is possible that the preliminary perfusion of saline solution would not have washed them free, but the fixing fluid might have dislodged them and caused them to form masses, such as those illustrated in figure 7.

COMMENT

The guinea pig, originating in South America, and living there in the Andes, may be somewhat more resistant to conditions of high altitude than other species. In a previous investigation [2] it was determined that guinea pigs can tolerate prolonged intermittent exposure to a barometric pressure simulating an altitude of 23,000 feet without serious consequences. No focal areas of degeneration were encountered in that series of experiments, and there were no generalized changes in the brain. The possible role of acclimatization to intermittent exposure to altitude was discussed. It was suggested that the pronounced increase in number of red blood corpuscles and hemoglobin values [12] could have acted as a protective mechanism to prevent structural changes in the brain. In the present study, some animals, intermittently exposed to a simulated altitude of 30,000 feet, exhibited structural changes in the brain after only one hundred or one hundred and fifty hours accumulated time. This period was too short for significant acclimatization to have taken place. Acclimatization after longer periods failed to prevent further damage.

Intermittent exposure to a simulated altitude of 30,000 feet for periods totaling as much as two hundred and fifty hours, surprisingly, produced no generalized pathologic changes in the brain, such as those described by other authors.[17] Most regions of the brain were indistinguishable from the same regions in the brains of control animals which were prepared simultaneously. It is evident, therefore, that most of the nerve cells of the brain were not damaged by the conditions of the experiment, and that they were structurally resistant to the anoxia prevailing at 30,000 feet.

The focal areas of shrunken cells or of impaired stainability did not always occur in the same places in the brain. Except in the case of

17. Hoff, Grenell and Fulton.[3] Morrison.[10]

the vermis of the cerebellum, which was consistently the site of true degeneration, areas of slight structural alteration appeared to be distributed in a chance fashion. A greater sensitivity of Purkinje cells and of the neurons of the cornu ammonis, which has been commonly reported, was not encountered. No evidence of gradients of susceptibility, under the conditions of the experiments, could be observed.

It would seem that damage to the brain occurred after prolonged intermittent exposure to reduced barometric pressures, such as those used in the present experiment, not because nerve cells were especially sensitive to the low partial pressures of oxygen, but because other factors tended to produce much more profound anoxia locally than the general environment imposed. The observation of leukostasis provided a clue. It may be suggested that impairment of blood flow occurred during the episodes of low pressure and that this slowing led to the leukostasis in some vessels; the neuronal changes followed whenever a critical level of stagnant anoxia was reached. It is interesting in this regard to consider the experiments of Knisley [18] on the stasis of white blood corpuscles in blood vessels.

Comparison of the results of the present study with those of other investigators reveals certain disparities. The generalized changes, such as vacuolation of cells, neuronophagia and widespread defects in stainability in nerve cells, were not encountered in the present experiment. The more extensive cerebral damage reported by others may be due in part to greater severity of their experimental conditions. On the other hand, many of the generalized changes which have been described are not entirely free from suspicion of being postmortem changes and/or fixation artefacts. There is no reason to labor this point at present. It will be considered at some length when studies on the effects of immersion fixation methods, now in progress, are completed.

The present experiments offer proof that retention of learning was impaired by intermittent anoxia; however, permanence of the defects was not established because the animals were killed soon after the last retesting. Further work on this subject is in progress.

Correlation of memory defects, length of time of exposure to anoxia and degree of cerebral damage is not so clearcut as it might have been had a much larger series of animals been studied. It is difficult to make a point for point correlation. However, it can be said that the most striking memory defects occurred in the group of animals which were carried to altitude in the chamber for the maximum accumulated time. It was this group also which most consistently showed marked structural changes in the brain. After only one hundred hours of

18. Knisley, M. H.; Eliot, T. S., and Block, E. H.: Sludged Blood in Traumatic Shock, Arch. Surg. **51**:220 (Nov.-Dec.) 1945.

elapsed time there was little indication of memory defects; correlatively, the brains of 2 of 3 animals which were studied histologically after one hundred hours showed little pathologic change, the exception being the single specimen which exhibited intramedullary hemorrhages. Some correlation was evident in the one hundred and fifty hour group, in which the 2 animals exhibiting focal areas of degeneration were likewise the animals which manifested the greatest alteration in retention of learning. The most striking pathologic change encountered was in the vermis of the cerebellum. This alteration would not seem to be related to the memory defects. The subtle changes which were seen as focal areas occurring more or less fortuitously throughout the brain might be related to the memory defects. It is more likely, however, that these changes were simply manifestations of a vascular phenomenon which in itself produced the memory defects, without severe and permanent destructive changes in the cerebral neurons. The histologic study failed to reveal an anatomic basis for defects in memory induced by intermittent episodes of anoxia.

SUMMARY

Young adult male guinea pigs were subjected to conditions simulating an altitude of 30,000 feet in a decompression chamber six hours daily and six days weekly for one hundred, one hundred and fifty, two hundred or two hundred and fifty hours. At appropriate times, the experimental animals and controls were killed by perfusion through the vascular system of a solution of formaldehyde to fix and preserve the nervous system and other organs in situ. Histologic technic was carefully controlled.

The animals responded to reduced barometric pressure by maintaining a quiescent state, usually with episodes of physical distress, collapse and, apparently, unconsciousness. After their removal from the chamber, comparison with controls rarely revealed significant behavioral or physical differences. No permanent neurologic defects could be observed. Some loss of weight occurred.

Twenty-four of the animals were trained to solve an alternation maze to the point of perfection. Four controls were picked at random from the superior half of a group of initial learners and 5 from the inferior half of this group. The rest of the animals were exposed to conditions of simulated altitude.

All animals were retested after one hundred hours at low pressure. No difference in retentive capacity between the control and the experimental group was noted at that time. After one hundred and fifty, two hundred and two hundred and fifty hours of decompression, groups consisting of 4 experimental animals showing the greatest signs of distress in the chamber at the time and 2 or more controls selected at

random were retested and then killed for study of pathologic changes in the brain. In all these retests, the controls exhibited perfect retention of memory, while all the experimental animals gave evidence of retentive loss. The most significant impairment of memory occurred in the samplings from the one hundred and fifty and two hundred and fifty hour groups; a closer correlation with pathologic alterations in the brain could be made in these groups than in the sampling from the two hundred hour group. However, all experimental animals in the two hundred hour group required retraining on the retest, whereas their controls did not.

Focal areas of degeneration occurred in the vermis of the cerebellum of all animals of the two hundred and two hundred and fifty hour groups and in 3 of the 7 animals studied in the one hundred and one hundred and fifty hour groups. Elsewhere in the brain, small areas of cell shrinkage or (less commonly) impaired staining occurred, fortuitously it seemed. For the most part, the tissues of the brain appeared normal, and most regions looked exactly like comparable regions in the control brains. The focal areas of degeneration or other structural change may have resulted from vascular stasis; leukostasis was encountered in the two hundred and fifty hour group.

The present experiments demonstrated that anoxia prevailing under the conditions of an altitude of 30,000 feet did not in itself cause demonstrable structural changes in the brain, but that it indirectly brought about focal defects. The impairment of memory occurred without specific correlation with pathologic changes in the brain.

University of Pennsylvania School of Medicine (Dr. Windle).
University of North Carolina School of Medicine (Dr. Jensen).
University of Washington Medical Department (Dr. Becker).

DYNAMIC ANATOMY OF THE CEREBRAL CIRCULATION

HENRY A. SHENKIN, M.D.
MEREL H. HARMEL, M.D.*
AND
SEYMOUR S. KETY, M.D.
PHILADELPHIA

SEVERAL recent suggestions [1] for the quantitative determination of the cerebral blood flow in man make the dynamic anatomy of the cerebral circulation [2] a necessary and timely study. Studies of the injected vascular beds in the cadaver have supplied information on the possible pathways of the cerebral circulation. In some important instances it is only by conjecture that conclusions have been drawn regarding the direction of flow, the sources of blood or the relative proportions in which the blood flows from these sources are combined. The present studies were performed on living man and therefore have the advantage of comprehending not only the anatomic pathways but also the dynamic circulatory patterns.

METHOD

Patients were selected for whom cerebral arteriographic studies were desirable in order that the possibility of a cerebrovascular lesion might be ruled out. Two of the 10 patients studied were found to have distinct pathologic lesions, and the data for these patients, which were distorted on that account, were excluded from consideration. One of these 2 patients had a large unilateral cerebral arteriovenous angioma, and the other had a large glioma on the left side.

In a complete study, 19 gage lumbar puncture needles were inserted through the intact skin into the superior bulb of each internal jugular vein, one external jugular vein and one femoral artery. The external jugular vein used was always on the side of the carotid arteries exposed for injection. The needles were

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* National Research Council Fellow in Anesthesiology.

From the Departments of Neurosurgery and Pharmacology, University of Pennsylvania School of Medicine.

1. (*a*) Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure and Normal Values, J. Clin. Investigation **27**:476 (July) 1948. (*b*) Gibbs, F. A.; Maxwell, H., and Gibbs, E. L.: Volume Flow of Blood Through the Human Brain, Arch. Neurol. & Psychiat. **57**:137 (Feb.) 1947. (*c*) Ferris, E. B., Jr.: Objective Measurement of Relative Intracranial Blood Flow in Man, ibid. **46**:377 (Sept.) 1941.

2. The term dynamic anatomy is used in connection with the cerebral circulation to denote the actual sources, directions and destinations of flow in the various vascular channels during life.

connected by tubing to a manifold, to which syringes were attached.[1a] Each system was kept from clotting by means of heparin. The carotid vessels of one side were exposed in the neck, and both the internal and the external carotid artery were sufficiently dissected that they could be identified clearly and that an injection into one or the other vessel could be made far enough distal to the bifurcation to insure against retrograde spread of the dye to the other vessel.

One cubic centimeter of Evans blue (T-1824), 0.1 per cent, was injected into either the internal or the external carotid artery. The injection was completed within one or two seconds, and samples of blood were taken simultaneously with the injection and over the ensuing fifteen to twenty seconds from the two internal jugular veins, the one external jugular vein and the femoral artery. This time limit was selected to insure complete flushing of the dye through the circulations involved. The concentration of the dye in the plasma of each sample was accurately measured by means of a Beckman photoelectric spectrophotometer, with correction for any possible hemolysis, according to the formula of Gibson and Evans.[3] Hemolysis was absent in every study but one.

After the injections of dye, a cerebral arteriographic study was performed, using 12 cc. of "thorotrast" (a colloidal suspension of thorium dioxide).

An approximate value for the extent of contamination of one vascular bed by another was obtained as the ratio of the plasma dye concentrations in the respective venous bloods. Thus, to measure the percentage by which blood in the internal jugular vein is contaminated with extracerebral blood, dye is injected into the external carotid artery, and samples of blood are taken from the internal jugular veins and the ipsilateral external jugular vein. If it is assumed that the sample from the external jugular vein represents the concentration of dye in the extracerebral blood, this concentration divided by the dye content of each internal jugular vein yields, after multiplication by 100, the percentage contamination.

Calculation of cerebral blood flow was attempted by means of injections of dye into the internal carotid artery on the basis of the Stewart principle[4]:

$$CBF = \frac{I}{(V-A)tH}$$

where CBF represents cerebral blood flow (cubic centimeters/minute); I, quantity of dye injected (milligrams); V, plasma dye concentration of internal jugular venous blood; A, plasma dye concentration in femoral arterial blood (milligrams/cubic centimeter); t, time over which samples are taken (minutes), and H, plasma hematocrit reading. This formula is valid (*a*) if the dye is evenly mixed with the cerebral venous blood, (*b*) if samples are taken at a constant rate over a period in which the dye is being completely washed out of the brain and (*c*) if the arterial sample is representative of blood entering the brain at the time of the sampling. The time interval was chosen as fifteen seconds, which was expected to be long enough for fairly complete washing out of the dye, yet short enough that recirculation of the dye would be negligible. It was found, however, that the dye was unevenly distributed in the cerebral venous return, so that it was necessary to average the dye concentration for the two internal jugular veins in an effort to compensate for

3. (*a*) Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Investigation **16**:301, 1937. (*b*) Gibson, J. G., Jr., and Evelyn, K. A.: Clinical Studies of Blood Volume: IV. Adaptation of Method to Photoelectric Microcolorimeter, ibid. **17**:153, 1938.

4. Stewart, G. N.: The Output of the Heart in Dogs, Am. J. Physiol. **57**: 27, 1921.

this difficulty. Gibbs, Maxwell and Gibbs [1b] previously reported measurements of cerebral blood flow by an alternative form of the Stewart principle.[4] The mathematical basis for these alternative applications of the Stewart principle to the brain has been discussed by one of us (S. S. K.).[5]

RESULTS

A complete study was obtained on only 3 patients because of inability to obtain samples from all four vessels throughout the

TABLE 1.—*Data on Complete and Partial Experimental Studies of Dynamic Circulatory Patterns in Ten Patients*

Patient	Injection Site*	Quantity Injected (Mg.)	Time of Sampling (Min.)	Homolateral External Jugular, Mg./100 Cc. of Plasma†	Right Internal Jugular, Mg./100 Cc. of Plasma†	Left Internal Jugular, Mg./100 Cc. of Plasma†	Plasma Hematocrit Reading
F. B.	R.E.C.	1.0	0.25	0.550	0.000	.....	0.60
C. S.	L.E.C.	1.0	0.25	0.800	.....	0.013	0.70
W. D.	L.I.C.	1.0	0.25	.....	0.830	1.020	0.55
D. M.	R.E.C.	1.0	0.25	1.870	0.041	0.018	0.60
	R.I.C.	1.0	0.25	0.143	1.260	0.665	0.60
J. M.	L.E.C.	1.0	0.25	1.433	0.011	0.000	0.68
	L.I.C.	1.0	0.32	0.114	0.705	.....	0.68
C. P.	L.E.C.	1.0	0.25	0.945	.....	0.005	0.64
	L.I.C.	1.0	0.25	0.161	.....	1.010	0.64
E. W.	L.E.C.	1.0	0.33	0.535	.....	0.000	....
W. J.	L.E.C.	1.0	0.25	0.546	0.009	0.027	0.63
	L.I.C.	1.0	0.25	0.234	0.441	0.540	0.63
H. D.	R.E.C.	2.0	0.25	0.905	0.044	0.013	0.52
	R.I.C.	1.0	0.25	0.196	0.845	0.122	0.52
L. J.	L.I.C.	1.0	0.25	.....	0.781	1.722	0.56

* R.E.C. indicates right external carotid artery; L.E.C., left external carotid; L.I.C., left internal carotid, and R.I.C., right internal carotid.
† After correction for recirculation by means of the simultaneous arterial blank.

TABLE 2.—*Distribution of Blood of the Internal Carotid Artery Between the Two Internal Jugular Veins*

Patient	Ipsilateral Internal Jugular Vein, per Cent	Contralateral Internal Jugular Vein, per Cent
W. D.	55	45
D. M.	66	34
W. J.	55	45
H. D.	87	13
L. J.	69	31
Mean	66	34

entire procedure. However, partial experiments were carried out on 7 additional patients, data on whom are pertinent to separate phases of the problem (table 1).

In 5 patients, samples from both internal jugular veins were obtained after injection of dye into one internal carotid artery (table 2), the

5. Kety, S. S.: The Quantitative Determination of Cerebral Blood Flow in Man, in Methods in Medical Research, Chicago, The Year Book Publishers, Inc., 1948.

results indicating that blood from a single internal carotid artery is unequally drained by the two internal jugular veins. On the average, 66 per cent of the blood from a single internal carotid artery drained by the internal jugular veins appeared in the ipsilateral internal jugular bulb, and 34 per cent appeared contralaterally.

In 5 patients, the external jugular venous blood was also successfully sampled after injection into the internal carotid artery on the same side. The results (table 3) indicate that an average of approximately 22 per cent of the blood flowing in an external jugular vein is derived from the

TABLE 3.—*Contamination of Blood of External Jugular Vein with Blood of Internal Carotid Origin*

Patient	Contamination, per Cent
D. M.	11.3
J. M.	16.2
C. P.	15.9
W. J.	43.0
H. D.	23.2
Mean	21.9

TABLE 4.—*Fraction of Total Blood Passing Through Internal Jugular Vein at Superior Bulb Which Has Extracerebral (External Carotid) Origin*

Patient	Ipsilateral Internal Jugular Vein, per Cent	Contralateral Internal Jugular Vein, per Cent	Total, per Cent*
F. B.	0.00	...	0.0
C. S.	1.60	...	3.2
D. M.	2.30	1.0	3.3
J. M.	0.00	0.8	0.8
C. P.	0.55	...	1.1
E. W.	0.00	...	0.0
W. J.	5.00	1.6	6.6
H. D.	4.80	1.4	6.2
Mean			2.7

* When samples from the ipsilateral vein alone were obtainable, the value was doubled to give the total contamination (probably an overestimate, since blood from the ipsilateral jugular vein usually showed the higher dye concentration).

ipsilateral internal carotid artery, and, therefore, presumably a significant fraction of the contents of the external jugular vein is cerebral venous blood.

In 8 patients, after injection of dye into the external carotid artery, samples taken from the jugular bulbs indicated that an average of only 2.7 per cent of the blood in the internal jugular veins was derived from extracerebral sources (table 4). The maximum amount of contamination of the blood of the internal jugular vein, with blood arising from the distribution of the external carotid artery (and hence presumably from extracerebral sources) was 6.6 per cent. The ipsilateral internal jugular vein usually contained a greater percentage of the

blood of the external carotid artery of one side than did the contralateral internal jugular vein.

In table 5 are presented calculated values for cerebral blood flow obtained by the dye dilution technic. Since the dye is not uniformly mixed in the cerebral venous return, but is recovered in higher concentration from the side of injection, values for blood flow calculated from the ipsilateral internal jugular vein are consistently lower than corresponding values for blood flow from the other internal jugular vein taken simultaneously. In an attempt to arrive at a closer approximation to the true flow, the dye concentrations in the two internal jugular veins were averaged and the cerebral blood flow was calculated from this pooled value.

TABLE 5.—*Calculation of Cerebral Blood Flow by Dye Dilution Technic*

Patient	From Ipsilateral Jugular Vein, Cc./Min.	From Contralateral Jugular Vein, Cc./Min.	Pooled Blood, Cc./Min.
W. D.	713	877	786
D. M.	530	1,010	692
W. J.	1,170	1,440	1,290
H. D.	908	6,300	1,590
L. J.	414	914	570
J. M.	...	653	...
C. P.	620	...	...
Mean	726	1,866	986
Mean N_2O*			756

* Mean value determined by the nitrous oxide technic on the basis of 1,400 Gm. of brain in normal males.[1a]

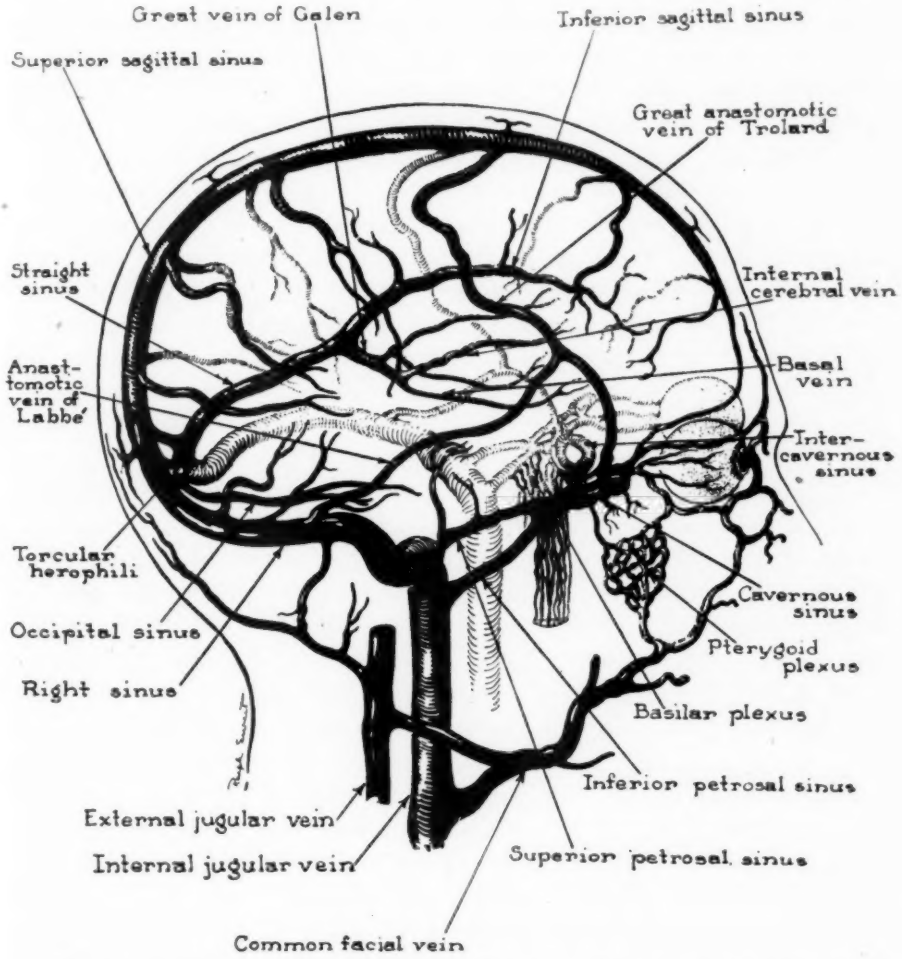
COMMENT

In order to discuss effectively the problem at hand, a brief review of the anatomy of the cerebral circulation is not out of place. This is particularly applicable to the venous drainage of the brain, since this topic is meagerly treated in the standard textbooks of anatomy.

In man, the paired common carotid arteries divide in the neck to form the internal and external carotid arteries on each side. The internal carotid artery ascends without branches into the cranium, where it first gives off the ophthalmic artery and a few insignificant vessels. Beyond the ophthalmic artery, the internal carotid artery supplies only cerebral structures, giving origin to the posterior communicating artery (occasionally large enough to be considered the posterior cerebral artery), the anterior choroidal artery and the anterior and middle cerebral arteries. Communication with the arterial supply of the opposite side is present between the two anterior cerebral arteries through the anterior communicating artery, and through the bifurcation of the basilar artery completing the circle of Willis. In man, unlike lower animals,[6] the external carotid arteries do not partici-

6. Wolff, H. G.: Cerebral Blood Vessels: Anatomical Principles, A. Research Nerv. & Ment. Dis., Proc. **18**:29, 1938.

pate in the blood supply of the brain. These vessels and their branches have no anastomotic connections with the vascular bed of the internal carotid artery except for a few minute and inconsequential twigs that pass from the dura (particularly anteriorly, close to the falx) to the cerebrum. It is clear, therefore, that any important mixing of the



The venous drainage of the brain (semidiagrammatic); drawing by Mr. Ralph Sweet, University of California Medical School.

blood of the brain and extracerebral structures, such as the face, scalp and skull, must occur, if it occurs at all, on the venous side of the circulation. On the venous side (figure), the cerebral cortical veins coursing on the cortical surfaces cross over the subdural spaces to empty into adjacent dural sinuses.

On the convex and medial surfaces of the brain there are eight to twelve pairs of veins passing to the superior sagittal sinus. These

may be divided into frontal, paracentral, central and occipital veins. The designation of these vessels as cortical veins has given rise to a misconception that these vessels drain only cortical tissue and therefore that the sagittal sinus conveys blood drained principally, if not only, from the cortex. However, as Cobb [7] pointed out, and as is repeatedly demonstrated at the operating table, these so-called cortical veins dip deep into the brain, well below the cortical layer, and establish free communication with the internal, or deep, cerebral veins. Any assumption that blood taken from the sagittal sinus is representative of venous drainage from the cerebral cortex must be evaluated in the light of this anatomic fact.

The inferior half of the brain has many large veins, the principal one being the middle cerebral vein, which runs in the lateral (sylvian) fissure and ends in the cavernous sinus. This large vessel also communicates with the superior sagittal sinus through the great anastomotic vein of Trolard and with the transverse sinus through the large vein of Labbé. The veins on the inferior surface of the frontal lobe pass partly to the inferior sagittal sinus and partly to the cavernous sinus. The inferior temporal veins supply partly the transverse and partly the superior petrosal sinus, the latter joining the lateral sinus to form the jugular bulb. The inferior occipital surface has a large vein (posterior cerebral vein) passing over the cerebral peduncle to join the great cerebral vein (of Galen) just before the latter enters the straight sinus.

The deep, or central, veins are drained principally through the great cerebral vein into the straight sinus. However, the free communications with the so-called cortical veins are not to be ignored. The paired internal cerebral veins, one from each hemisphere, form the great cerebral vein; the latter receives the posterior cerebral vein (mentioned previously) and veins from the upper surface of the cerebellum and then flows into the straight sinus. These paired internal cerebral veins are formed by the confluence of the choroid vein and the vena terminalis. The posterior cerebral vein also receives the basal vein, the thalamic vein and veins from the choroid plexus of the third ventricle, corpus callosum, pineal region and area of the posterior horn of the lateral ventricle. The terminal vein drains the region of the corpus striatum, thalamus, fornix, septum pellucidum and anterior horn of the lateral ventricle. The choroid vein drains the choroid plexus of the lateral ventricle, the hippocampus, the inferior horn of the lateral ventricle, the fornix and, in part, the corpus callosum. The basal vein drains the insula, opercular gyri, corpus striatum, anterior cerebral vein and interpeduncular structures.

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7. Cobb, S.: The Cerebrospinal Blood Vessels, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932.

The cerebellar veins are divided into a superior and an inferior group. The latter, larger than the former, pass partly to the inferior petrosal and transverse sinuses and partly to the occipital sinus. The superior cerebellar veins pass partly to the straight sinus and great cerebral vein and partly to the transverse and superior petrosal sinuses. The veins of the medulla and pons terminate in the inferior petrosal and transverse sinuses.

The principal dural sinuses, collecting blood from the aforementioned sources, join to form the torcular Herophili. Thus, the superior sagittal sinus and the straight sinus, the latter representing the junction of the inferior sagittal sinus and the great cerebral vein, adjoin. The two lateral sinuses take origin from the region of the torcular, ultimately to reach the jugular bulbs. The cavernous and circular sinuses, at the base of the brain, have equally free commnication from side to side and drain through the petrosal sinuses to the jugular bulbs, and via the basilar plexus to the longitudinal veins in the spinal canal.

In contrast to the arterial pattern, the venous drainage of the brain has numerous, but small, communications with extracerebral pathways. These are the so-called emissary veins, the most prominent being the mastoid emissary vein, the less constant parietal emissary vein, the veins passing through the foramens of the base of the skull and the orbits and the veins which communicate with the pterygoid plexus.

From the outline of the anatomy of the cerebral vascular pathways presented here, it may be noted that various opportunities are present for the intermingling of the circulation from each of the cerebral hemispheres, from cortex and subcortical tissue and from the brain as a whole and the extracerebral structures. The degree to which these pathways are actually utilized in the living brain is the problem to the solution of which the present studies are particularly pertinent.

Mixing Across the Midline.—On the arterial side, the circle of Willis is generally regarded as a channel in which arterial blood, entering by way of the major vessels, is mixed and distributed throughout the brain. That this is not true in living animals was first demonstrated by Kramer,[8] who found that india ink injected into one internal carotid artery was deposited almost exclusively in the ipsilateral hemisphere. Further, it is now common experience in the routine performance of cerebral arteriography that the radiopaque medium outlines the vessels only on the side of injection. Our own findings of a significant disproportion of recovered dye in favor of the internal jugular vein on the side of injection of the carotid artery confirms these observations. This is what one would expect on the basis of simple hemodynamics. The pressures in the two halves of the circle of Willis

8. Kramer, S. P.: On the Function of the Circle of Willis, J. Exper. Med. **15**:348, 1912.

normally being equal, there would exist no pressure gradient across the communicating channels. The circle of Willis, therefore, is only a potential anastomotic channel, brought into play when one of its contributing vessels is obstructed.

On the venous side, the large dural sinuses in the midline drain both hemispheres, dividing their contents at the torcular, and the blood is conveyed to the jugular veins via the lateral sinuses. This would seem to permit almost complete mixing of the venous drainage from the two hemispheres. As a matter of fact, however, our results reveal that two thirds of the blood supplied to one hemisphere through an internal carotid artery is actually drained through the ipsilateral internal jugular vein. The anatomic basis for this observation is undoubtedly in the many tributaries passing directly to the lateral and petrosal sinuses, which join to form the bulb of the jugular vein. These veins, draining ipsilaterally, are, principally, the inferior cerebral veins, from the temporal lobe and the under surfaces of the occipital and frontal lobes, and the great vein of Labbé, which drains the lateral surface of the hemisphere.

Cortical-Subcortical Mixing.—Although, as demonstrated previously, each internal jugular vein carries blood predominantly derived from the hemisphere of the same side, there is reason to believe that the drainage from the various histologic regions of the brain are intimately mixed by the time the jugular bulb is reached. Despite a prevalent belief in the absence or incompleteness of a true confluence of the sinuses in man,[9] the best studies on the anatomy of the torcular, by Edwards [10] and by Manno,[11] each of whom studied 50 cases, showed that in the majority of instances (64 and 72 per cent, respectively) true mixing of blood from the sagittal and the straight sinus should occur. The straight and the superior sagittal sinus may join, with immediate separation into lateral sinuses, or the two sinuses may first bifurcate and each division join with a division of the other to form a lateral sinus. Only in one third of the cases was there predominant drainage of the sagittal sinus into one lateral sinus and the straight sinus into the other, and in these cases communication between the two always existed.

But, even in the minority of cases in which a complete confluence is absent, the torcular is only one of many means whereby mixing may occur between cortical and subcortical venous blood. In the first

9. Himwich, W. A.; Homburger, E.; Maresca, R., and Himwich, H. E.: Brain Metabolism in Man: Unanesthetized and in Pentothal Narcosis, Am. J. Psychiat. **103**: 689, 1947.

10. Edwards, E. A.: Anatomical Variations of the Cranial Venous Sinuses, Arch. Neurol. & Psychiat. **26**:801 (Oct.) 1931.

11. Manno, cited by Edwards.[10]

place, as was previously pointed out, the venules which emerge from the cortex destined for the superior sagittal sinus are continuous with those which pass through the subcortical regions to drain eventually into the straight sinus; there is thus no clearcut differentiation of cortical and subcortical blood, even at their origin. In the light of the venous anatomy reviewed here, there exist in the larger veins of the brain many opportunities for mixing of blood exclusive of the torcular. Thus, what has been considered "cortical blood" drains via the inferior cerebral veins and the anastomotic veins of Trolard and Labbé and from half the cerebellar cortex into each lateral sinus beyond the torcular. Our experiments with injection of dye demonstrated that the unilateral drainage beyond the torcular constitutes about one third of the jugular venous blood. Likewise, "subcortical blood" drains equally to the two jugular veins beyond the torcular from the cerebellum, the pons and the medulla. Thus, the anatomic basis for incomplete mixing of blood across the midline is one of the important factors assuring mixing of the drainage from various histologic regions.

Since, from the smaller architectural vascular units through the major dural sinuses there is little opportunity for separation of the cortical and the subcortical venous outflow, it is difficult to understand how inferences regarding the individual metabolisms of the two components of the brain tissue can be drawn from analysis of samples from the left and the right jugular vein.[9] In at least one series of 10 studies no significant difference was found for cerebral blood flow or oxygen consumption in simultaneous measurements on the right and the left internal jugular vein.[1a]

Cerebral and Extracerebral Mixing.—On the arterial side, there is no significant communication between the internal and the external carotid vascular bed. On the other hand, in the venous circulation, the emissary veins offer a possible communication. It is of importance to ascertain the extent and direction of the flow in these communications between the two venous beds.

Our studies revealed that approximately 22 per cent of the blood flowing in the external jugular vein is derived from the brain (table 3). On the other hand, an average of only 3 per cent of the blood in the jugular bulb is derived from extracerebral structures (table 4). The great discrepancy in these figures indicates that the flow of blood in the cerebral-extracerebral pathways is predominantly away from the brain, and for practical purposes the jugular bulb is free of blood of extracerebral origin. This is entirely in accord with hemodynamic necessity. In a series of 5 consecutive observations (table 6), it is seen that in both the horizontal and the sitting position the cerebrospinal fluid pressure is consistently greater than the pressure in the

external jugular vein by an average of 7.9 and 10.3 cm. of water, respectively, for the two positions. In order for blood to pass from the facial circulation to the intracranial veins by way of emissary veins, it would have to travel against a large pressure gradient. Thus, data in tables 4 and 6 show that contamination of internal jugular venous blood with blood of extracerebral origin should not, and in fact does not, occur to any significant extent. If one regards the eye and its appendages as extracerebral tissue, this statement must be modified. Being supplied by the internal carotid artery and drained principally via the cavernous sinus, orbital blood reaches the internal jugular vein and would not have been measured in these studies.

The understanding of the dynamics of the cerebral circulation gained in these studies has practical significance in the evaluation of several suggested methods for the measurement of the cerebral blood flow in man.

TABLE 6.—*Hydrostatic Difference in Pressure Between the Cerebrospinal and the External Jugular System Measured Simultaneously*

Patient	Cerebrospinal Pressure Minus External Jugular Venous Pressure, Cc. of Water	
	Horizontal Position	Sitting Position
1	7.9	6.0
2	5.1	5.5
3	8.7	11.2
4	11.0	17.8
5	6.7	11.0
Mean	7.9	10.3

In 1941, Ferris [1e] devised an ingenious technic for the objective measurement of relative intracranial blood flow in man, based on the plethysmographic principle. By occluding the veins of the neck for a few seconds and measuring simultaneously the displacement of spinal fluid through a needle of large caliber inserted into the lumbar subarachnoid space, a measure is obtained of the net intracranial accumulation of blood. This method has been critically evaluated by Gregg and Shipley.[12] Our observations confirm one of their basic objections. Since even in normal circumstances, with no interference in cerebral venous drainage, there is a significant overflow of cerebral venous blood into the veins of the face, it would be expected that with the internal jugular veins occluded an even greater fraction of cerebral drainage would go via the emissary vessels to the freely distensible tissues of the face. This source of error plus the drainage via the

12. Gregg, D. E., and Shipley, R. E.: Experimental Approaches to the Study of the Cerebral Circulation, Federation Proc. **3**:144, 1944.

unoccluded spinal channels [13] may explain the inordinately low estimates of intracranial blood flow yielded by this technic.

In 1945 the nitrous oxide method for the quantitative determination of human cerebral blood flow was reported.[14] This method represents an adaptation of the Fick principle to the dynamic relation of the uptake of an inert gas by an organ. Its application to the brain depends on the possibility of obtaining from a single internal jugular vein, at the level of its superior bulb, representative samples of cerebral venous blood not significantly contaminated by blood from extracerebral sources. We have already shown that the blood in either jugular bulb is representative of the drainage from all the histologic regions of the brain, and, therefore, the values obtained from such samples would be an approximate average of the whole. However, because the hemisphere to hemisphere communication is incomplete, it should be pointed out that in the presence of disease confined to one hemisphere and affecting its metabolism or blood flow, these changes would be partially reflected in samples of blood from the jugular vein on that side. Our studies with injection of dye have demonstrated that contamination of blood of the internal jugular vein with blood of the external carotid artery (extracerebral) origin is relatively insignificant. A further source of contamination, not in the scope of this study, is the drainage from the orbital apparatus. This, together with the average contamination of 2 per cent from drainage from the external carotid artery, probably explains the slight deviations from the ideal uncontaminated curve which are frequently observed in measurements of cerebral blood flow with the nitrous oxide method.

More recently, an adaptation of the Stewart principle to the human cerebral circulation has been made by Gibbs, Maxwell and Gibbs.[1b] This method depends on the adequacy with which a dye injected into one internal carotid artery is mixed with the total cerebral circulation by the time it arrives at an internal jugular vein. Our results indicate that such mixing is far from complete and that, on an average, two thirds of the dye appears in the internal jugular vein on the side of injection. If samples from both jugular veins are taken and the results pooled, a better approximation to the true cerebral circulation should be obtained. It is interesting to note that the average for such determinations on the patients here reported (986 cc. per minute) corresponds reasonably well with the average normal value obtained by means of the nitrous oxide technic for a brain of average weight (756 cc. per minute), especially since the lower figure was obtained

13. Batson, O. V.: Function of Vertebral Veins and Their Role in Spread of Metastasis, Ann. Surg. **112**:138, 1940.

14. Kety, S. S., and Schmidt, C. F.: Determination of Cerebral Blood Flow by the Use of Nitrous Oxide in Low Concentrations, Am. J. Physiol. **143**:53, 1945.

on comfortably resting subjects and the higher one during an operation, with the use of local anesthesia. Furthermore, the ophthalmic blood flow and other extracerebral contamination would affect each method differently, so that the blood flow through purely cerebral tissue would be overestimated with the dye dilution method and somewhat underestimated with the nitrous oxide method.

SUMMARY

By means of dye injection technic in living human subjects, the partition and distribution of the circulation of the head were studied.

Evidence is presented that blood entering the brain via each internal carotid artery is distributed almost wholly to the ipsilateral hemisphere and drained predominantly by the internal jugular vein on the corresponding side.

Evidence is presented that blood in each internal jugular vein is fairly representative of the drainage from all the histologic components of the brain.

The data indicate that blood in the internal jugular vein at the level of the superior bulb is relatively free of blood derived from extracerebral sources. On the other hand, blood in the external jugular vein contains a significant fraction of cerebral venous blood.

In 7 patients, the total cerebral blood flow was estimated by a dye dilution technic from samples obtained simultaneously from the internal jugular bulbs.

The relation of these findings to various suggested methods for measuring human cerebral blood flow is discussed.

STUDIES ON HEADACHE

Analysis of Vascular Mechanisms in Headache by Use of the Human Centrifuge, with Observations on Pain Perception Under Increased Positive G

E. CHARLES KUNKLE, M.D.*
DURHAM, N. C.

CAPTAIN DOUGLAS W. LUND
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
CAPTAIN PHILIP J. MAHER
UNITED STATES AIR FORCE

IN 1796 Erasmus Darwin,[1] grandfather of the naturalist, proposed an inquiry into the effects which "whirling a person" at the end of a revolving beam might have on certain symptoms of disease, particularly headache. The preliminary results of such an analysis, begun a century and a half later, and using a modern man-carrying centrifuge, have been presented briefly elsewhere, and are described in detail in the present report.[2]

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* Lewis Cass Ledyard Jr. Fellow in Medicine.

From the New York Hospital and the Department of Medicine, Cornell University Medical College, New York, and the Army Air Forces Aero Medical Laboratory, Air Materiel Command, Wright Field, Ohio.

1. Darwin, E.: Zoonomia, ed. 4, Philadelphia, Edward Earle, 1796, vol. 2. It had been reported to Darwin that were a man to ride outstretched on the revolving stone of a corn mill, he would soon detect a pleasant state of drowsiness. This casual observation Darwin thought might indicate a potential remedy for the restlessness associated with febrile illnesses: "Another experiment I have frequently wished to try, which cannot be done in private practice, and which I therefore recommend to some hospital physician . . . is to endeavor to still the violent actions of the heart and arteries . . . by gently compressing the brain. This might be done by suspending a bed so as to whirl the patient round with his head most distant from the center of motion, as if he lay across a mill-stone."

In another passage Darwin speculated even more freely about centrifugal force applied in the opposite direction: "What might be the consequence of whirling a person with his head next the centre of motion, so as to force the blood from the brain into the other parts of the body, might [also] be discovered by cautious experiment without danger. . . . Would a circulating bed remove any kind of headache?"

2. Wolff, H. G.; Kunkle, E. C.; Lund, D. W., and Maher, P. J.: Studies on Headache: Induced Mechanical Stresses in the Analysis of Headache Mechanisms, Tr. Am. Neurol. A., 1947, p. 93.

The observations here presented chiefly concern the effects of centrifugal forces on certain experimentally induced and clinical headaches. Incidental to the main investigation, studies were made on headache induced by centrifugal forces, illustrating in an unusual way the importance of vascular mechanisms in headache. Also incidental, but essential to the interpretation of the studies on headache, was an investigation of the effects of centrifugal forces on pain perception per se.

The behavior of the human subject exposed to accelerations and centrifugal forces, with special reference to the problems of high speed flight, has been outlined in recent reviews, particularly those by Ham [3] and by Wood, Lambert, Baldes and Code.[4] The types of such forces pertinent to this discussion are those most important to the pilot, i. e., forces directed in the long axis of the body. Man at rest or moving at constant velocity is subject only to the force of gravity. This convenient unit of force, the g, will impart to a body on which it freely acts an acceleration of 32.2 feet (980.616 cm.) per second per second. Such a force acting on man in the head to foot direction (or on sitting man, in the head to seat direction) is defined by common usage as "1.0 positive g," or + 1.0 g. When the pilot in flight abruptly changes the direction of his airplane, as in a "pull out" from a dive, his momentum imposes on him a centrifugal force in the head to seat direction of several positive g's. Similar increases in positive g are induced under controlled conditions in the human subject spun on a centrifuge with his head directed toward the center of rotation.

The sensations observed during such a stress are at first only those of heaviness of the head and body and sagging of the loose tissues of the face. More significant are the circulatory changes which ensue, for, although the arterial pressure at heart level is well maintained under increased positive g, the "weight" of the column of arterial blood above the heart is greatly increased, and at forces of approximately 5 g or more may so effectively oppose the systolic pressure that cranial circulation is virtually halted. In consequence, under sufficiently high positive g maintained for several seconds, there is a phase of progressive failure in vital cranial functions. This is evidenced first by narrowing of the visual fields or by complete blindness (black-out), due to retinal ischemia, and then by loss of consciousness, due to cerebral ischemia. After the first seven or eight seconds, however, pressor reflexes, arising mainly from the carotid sinus, become fully operative and usually lead to some degree of recovery of cranial functions. The blood pressure at heart level in this phase

3. Ham, G. C.: Effects of Centrifugal Acceleration on Living Organisms, War Med. **3**:30, 1943.

4. Wood, E. H.; Lambert, E. H.; Baldes, E. J., and Code, C. F.: Effects of Acceleration in Relation to Aviation, Federation Proc. **5**:327, 1946.

rises to hypertensive levels, although the pressure at head level still remains below normal. Of considerable practical significance is the fact that the subject who consciously or unconsciously tenses his muscles provides for himself a partial protection against the circulatory effects of increased positive g. Hence, in general, g tolerance varies inversely as the degree of bodily relaxation.

When the subject is under negative g (seat to head force), the changes in the circulation are for the most part in the opposite direction and are far less tolerable. As noted by a pilot in an infrequently attempted maneuver, an outside loop, or by the subject riding the centrifuge with head away from the center, the vessels of the face become congested, presumably as a result of rises in arterial and venous pressures at head level.[5] Even in brief exposures to negative g as low as 3.0, hemorrhages may occur in the skin of the face and beneath the conjunctiva.

From the facts thus summarized, it is evident that headache arising from distension of, or traction on, pain-sensitive cranial vessels might be altered by centrifugal forces. Headaches particularly suitable for such an analysis would seem to be those produced by distention of intracranial or extracranial arteries. Headache induced by histamine, for example, is the familiar prototype of vascular headache. Arising from dilated branches of the internal carotid arteries, this headache is reduced in intensity or abolished either by elevation of the extravascular (cerebrospinal fluid) pressure or by a lowering of the cranial and systemic blood pressures by a second injection of histamine.[6] Similarly, migraine headache, which arises from distention of cranial arteries, is transiently reduced in intensity by an injection of histamine, or for a longer period by the administration of vasoconstrictor drugs.[7] Thus, methods for manipulating the state of distention of cranial arteries have been highly useful in defining vascular mechanisms in headache. Hence it is pertinent to ask: "Can headache arising from distention of cranial arteries be eliminated by a reduction of cranial blood pressure under increased positive g?"

To be distinguished from the circulatory effects of increased positive g is a traction effect by which headache may sometimes be produced. This hypothesis rests on the following considerations: The human

5. Armstrong, H. G., and Heim, J. W.: The Effect of Acceleration on the Living Organism, J. Aviat. Med. **9**:199, 1938.

6. Clark, D.; Hough, H., and Wolff, H. G.: Experimental Studies on Headache: Observations on Headache Produced by Histamine, Arch. Neurol. & Psychiat. **35**:1054 (May) 1936.

7. Sutherland, A. M., and Wolff, H. G.: Experimental Studies on Headache: Further Analysis of the Mechanism of Headache in Migraine, Hypertension and Fever, Arch. Neurol. & Psychiat. **44**:929 (Nov.) 1940.

brain, weighing approximately 1,300 Gm. and with a specific gravity of 1.041, is immersed in cerebrospinal fluid of a specific gravity of 1.007. The brain is anchored to the skull by the transdural veins, which lie mainly over the convexities, and by the major arteries at the base.[8] A headache probably arising from traction on certain of these vessels can be induced in the normal subject by vigorous rotary head movements to one side or the other.[9] During exposure to increased positive g, as observed through cranial windows in animals, a caudad displacement of the brain tends to occur.[10] Such a shift, it has been stressed, is likely to be slight because of the nearly equal densities of the brain and the surrounding fluid and because of the unyielding bony floor and sides of the cranial cavity.[11] That this displacement may nonetheless be of practical significance is suggested by the occasional development of headache during repeated or intensive exposures to increased positive g.[12]

In Clark's experience, moreover, the headaches infrequently noted during prolonged centrifugation were made worse during intermittent straining, an observation strongly supporting the suspicion that cranial vessels were the sources of the pain.[13] In the absence of other specific data, however, the hypothesis that such headache arises from caudad traction by the brain on anchoring arteries and veins must remain open to question.

On the other hand, another uncommon symptom of centrifugal force, a headache noted during the period of release from increased positive g, is more readily accessible to analysis. For, as will be outlined later in this report, such "release" headache can be related to

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8. (*a*) Batson, O. V.: Anatomical Problems Concerned in the Study of Cerebral Blood Flow, Federation Proc. **3**:139, 1944. (*b*) Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Pain-Sensitive Structures on the Head and Their Significance in Headache, Arch. Surg. **41**:813 (Oct.) 1940. (*c*) Kunkle, E. C.; Ray, B. S., and Wolff, H. G.: Studies on Headache: An Analysis of the Headache Associated with Changes in Intracranial Pressure, Arch. Neurol. & Psychiat. **49**:323 (March) 1943.

9. Holbourn, A. H. S.: Mechanics of Head Injuries, Lancet **2**:438, 1943. Hyslop, G. H.: Rapid Head Movement Test of Equilibratory Function, Arch. Neurol. & Psychiat. **52**:140 (Aug.) 1944. Kunkle and others.[8a]

10. Jasper, H. H., and Cipriani, A. J.: Physiological Studies on Animals Subjected to Positive G, J. Physiol. **104**:6, 1945.

11. Franks, W. R.; Kerr, W. K., and Rose, B.: Some Neurological Signs and Symptoms Produced by Centrifugal Force in Man, J. Physiol. **104**:10, 1945.

12. (*a*) Stewart, W. K.: Some Observations on the Effect of Centrifugal Force in Man, J. Neurol., Neurosurg. & Psychiat. **8**:24, 1945. (*b*) Ceres, F.: Aviation Medicine in the United States Navy, War Med. **1**:43, 1941. (*c*) Rook, A. F., and Dawson, D. J.: Hypotension and Flying, Lancet **2**:1503, 1938.

13. Clark, W. G.: Personal communication to the authors.

accompanying circulatory changes in the head and uniquely demonstrates a vascular mechanism in headache.

Essential to an accurate evaluation of the studies on headache is knowledge of the effect of increased positive g on pain perception per se. If, as a result of diminished cerebral circulation, the threshold to pain were appreciably elevated or pain intensity were dulled, an improvement in headache during centrifugation would be nonspecific and could not necessarily be ascribed to an alteration in the mechanism of the headache. A review of the various sensory functions which have been studied during acute cerebral anoxia [14] or during exposure to increased positive g [15] indicates that pain sensation has apparently been neglected. Accordingly, preliminary to the studies on headache, the effect of increased positive g on pain perception was investigated. Since this topic logically precedes the analysis of headache in relation to centrifugal forces, it will be considered first in the presentation of data.

THE HUMAN CENTRIFUGE

The mechanical stresses required in these experiments, always increased positive g, were induced by the human centrifuge of the Army Air Forces Aero Medical Laboratory at Wright Field, Ohio (fig. 1). This instrument consists essentially of a cab suspended from a horizontal beam 20 feet (6.1 meters) from a vertical axis, which is turned by a 180 horse power electric motor. Automatic control is accomplished by means of a photoelectric seeking mechanism, which follows a preplotted g curve drawn in black ink on a strip of white paper. The centrifuge accelerates rapidly and smoothly, reaching the peak g in periods as short as three seconds if desired. As the angular velocity increases, the cab rotates on its own axis so as to direct the head of its seated occupant toward the center of the centrifuge. A horizontal platform at the opposite end of the revolving beam is used if the subject is to be exposed to positive g in the supine position. An observer rides on a central platform surrounding the axis. All runs are carried out in a darkened chamber. The controlling and the recording apparatus are in an adjacent room.

EXPERIMENTAL SUBJECTS

The subjects for the investigations of induced headache and other types of pain were 8 men between the ages of 24 and 36, all veterans of g experiments. The studies on clinical headache included 3 additional adult subjects, 2 of whom were women and none of whom had ever before ridden the centrifuge.

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14. Rossen, R.; Kabat, H., and Anderson, J. P.: Acute Arrest of Cerebral Circulation, Arch. Neurol. & Psychiat. **50**:510 (Nov.) 1943.

15. Burmeister, H.: Untersuchungen über Aenderungen der optischen Reaktionszeit des Menschen beim Einwirken hoher Fliehkräfte, Luftfahrtmedizin **3**: 277, 1939. Livingstone, P. C.: The Problem of Black-Out in Aviation (Amaurosis Fugax), Brit. J. Surg. **26**:749, 1939. Ham.[3] Wood and others.[4] Armstrong and Heim.[5] Stewart.[12a]

METHODS AND RESULTS

I. PAIN PERCEPTION DURING INCREASED POSITIVE G

Methods.—For the study of the effect of increased positive g on pain perception, stimuli of several types were employed. The principal tests were made with pains induced by radiant heat because of the proved suitability of this technic for measuring the pain threshold and for eliciting suprathreshold pains of reproducible intensities.[16] The method depends on the verbal report of an instructed subject. In the modified Hardy-Wolff-Goodell apparatus used, a beam of light from a 500 watt lamp is directed through a circular aperture 12.5 mm. in diameter.[17] The intensity of the predetermined stimulus is expressed in millicalories per second per square centimeter, read directly from the voltmeter of the control unit. An electronically controlled shutter permits exposure to the heat stimulus for a selected time, in these experiments always three seconds. The pain threshold stimulus is defined as that stimulus in response to which barely perceptible pain is added to the sensation of heat at the end of the three second period.

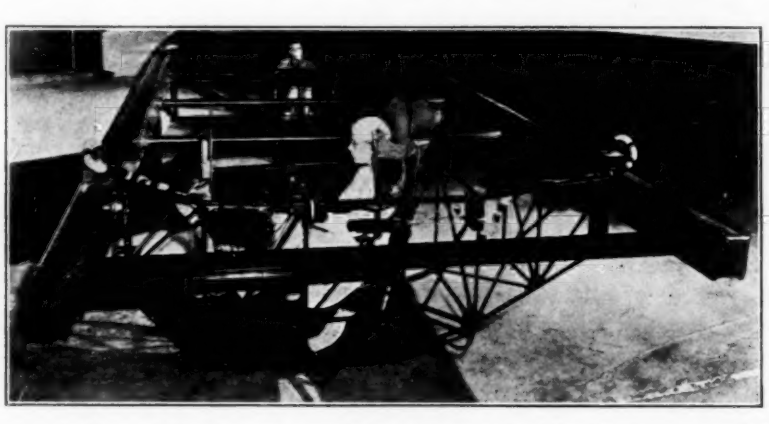

Fig. 1.—View of the human centrifuge of the Army Air Forces Aero Medical Laboratory, Air Materiel Command. The cab, upright when at rest, is in the foreground.

Each experiment with pain threshold measurements consisted, first, in a determination of the threshold with the subject seated at rest in the centrifuge cab, his left forearm held comfortably flexed at the level of the xiphoid, with the volar surface resting snugly against the aperture of the stimulator. Measurements were then repeated during centrifugation, the heat stimulus being inserted from the fourth through the sixth second, the period in which the circulatory effects of positive g are generally maximal, or nearly so.

With the same instrument, moderately severe pains were predictably induced by heat stimuli well above the threshold levels. The intensity of each pain was estimated by the subject in units, here termed "dols," on a 10 point scale, on which

16. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain: A New Method for Measuring Pain Threshold; Observations on Spatial Summation of Pain, J. Clin. Investigation **19**:649, 1940.

17. The apparatus is constructed by the Experimental Engineering Company, Bergenfield, N. J.

10 dols represents maximal pain.[18] The chosen stimulus was then repeated during the fourth through the sixth second of centrifugation, and the intensity of the resultant pain was compared with that of the control pain.

In addition, sustained pains of high intensities were induced by local cooling of a finger immersed in a mixture of crushed ice and water at a temperature of 0 C.,[19] or by the intramuscular injection of hypertonic (5 per cent) solution of sodium chloride.[20] Control curves of the rise and fall of the induced pains were charted for comparison with the course of the pain when the stimulus was repeated on a subsequent day, and increased positive g was applied for fifteen seconds at or near the peak of the pain experience.

Results.—In 12 experiments on 8 subjects, the pain threshold was found to be essentially unaffected by exposure to +3.0 or +4.0 g. Minor rises or falls in the threshold were observed, but the changes usually lay within the range of experimental error. In 12 experiments on 5 subjects, the intensities of induced pains were only slightly diminished during centrifugation at +3.0 or +4.0 g. In the observations on sustained pains, moreover, the slight improvement frequently was reported as soon as the centrifuge began to revolve and lasted only through the first few seconds of the experimental period.

Comment.—It is evident that exposure to +3.0 to +4.0 g generally exerts little or no effect on the threshold to pain or the intensity of pain. The minor reductions in the intensity of sustained pains occurred so early in the period of centrifugation as to suggest that distraction was probably the major factor in the improvement. Hence, in the experiments of the next section, a reduction in the intensity of a headache on the centrifuge can be attributed to the mechanical effect of the centrifugal force only if the change in the headache is pronounced and coincides with the actual application of increased g.

II. EFFECTS OF INCREASED POSITIVE G ON HEADACHES OF VARIOUS TYPES

A. Experimentally Induced Nonvascular Headaches.

Methods.—By means of a cloth band, 2.0 cm. in width, tightly encircling the head from brow to occiput, headache of moderate intensity (4 dols) was induced in each of 2 male subjects. The pain in each was predominantly frontotemporal. In 1 of these subjects, on another occasion, a severe right temporal headache

18. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain: Discrimination of Differences in Intensity of a Pain Stimulus as a Basis of a Scale of Pain Intensity, J. Clin. Investigation **26**:1152 (Nov.) 1947.

19. Wolf, S., and Hardy, J. D.: Studies on Pain: Observations on Pain Due to Local Cooling and on Factors Involved in the Cold Pressor Effect, J. Clin. Investigation **20**:521, 1941.

20. Lewis, T.: Suggestions Relating to the Study of Somatic Pain, Brit. M. J. **1**:321, 1938.

was induced by the injection into the temporal muscle of 0.1 cc. of 5 per cent solution of sodium chloride. During the height of the headache each subject was then exposed to + 3.0 g for periods of thirteen to seventeen seconds.

Results.—In both subjects the "band" headaches were transiently and slightly reduced in intensity, beginning early in the centrifuge run. The sequence of events is shown diagrammatically in figure 2A. The intensity of the "temporal muscle" headache also diminished only slightly (fig. 2 *B*).

Comment.—In their limited responses to the experience on the centrifuge, these nonvascular headaches behaved essentially as did pains induced in the finger or arm. The slight, brief improvement

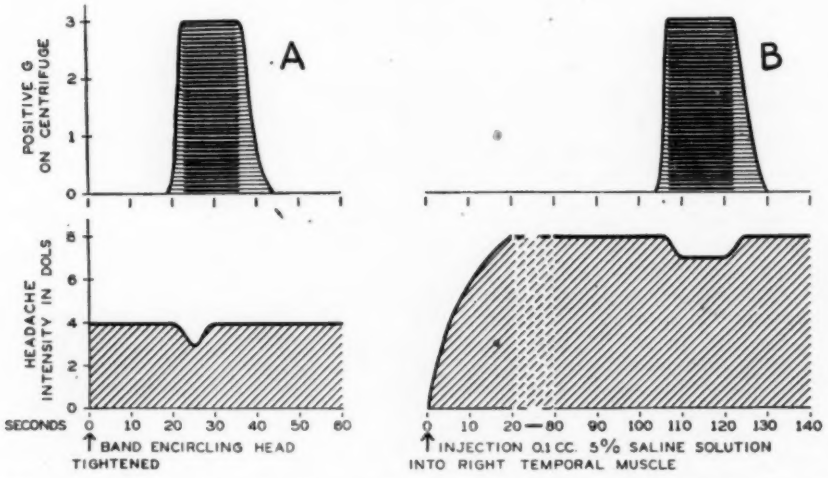

Fig. 2.—Slight reduction in the intensity of experimental headaches of nonvascular origin during centrifugation at a positive acceleration of 3.0 g: *A* (male subject, aged 24), headache induced by a band compressing the circumference of the head; *B* (male subject, aged 31), headache induced by the intratemporal injection of a hypertonic solution of sodium chloride.

noted in each headache under increased positive g can probably be ascribed to distraction.

B. Experimentally Induced Vascular Headaches.

Methods.—The effect of centrifugal force on headache induced with histamine injected intravenously was observed in three experiments on 2 subjects. Control trials had indicated that the injection of 0.09 to 0.1 mg. of histamine phosphate U. S. P. sufficed to yield in each trial a moderately severe, throbbing, generalized headache, lasting three to six minutes. Exposures to centrifugal forces of + 2.0 to + 3.6 g for fifteen seconds were introduced at the peak of the headache, approximately one hundred seconds after the injection of the histamine.

Caffeine-withdrawal headache was induced in 2 other subjects by the method of Dreisbach and Pfeiffer, i. e., the abrupt suspension of all use of caffeine after

the drug had been administered in increasing amounts for nine days.[21] The headache, developing eighteen hours after caffeine was withdrawn, was mild and frontal in 1 subject and moderately severe and generalized in the other. In both subjects the pain was easily aggravated by sudden rotation of the head.

Results.—In two exposures at + 3.0 g and one at + 3.6 g, headaches of moderate intensity induced with histamine were completely eliminated. The relief usually began as the peak g was reached and lasted until the centrifuge came to a stop, the pain then returning and rising slowly to its former intensity or one of slightly less severity. The data from an experiment at an acceleration of + 3.0 g are summarized in figure 3. During acceleration of + 2.0 g a histamine headache of 5 dols was nearly, but not entirely, eliminated. On repetition of

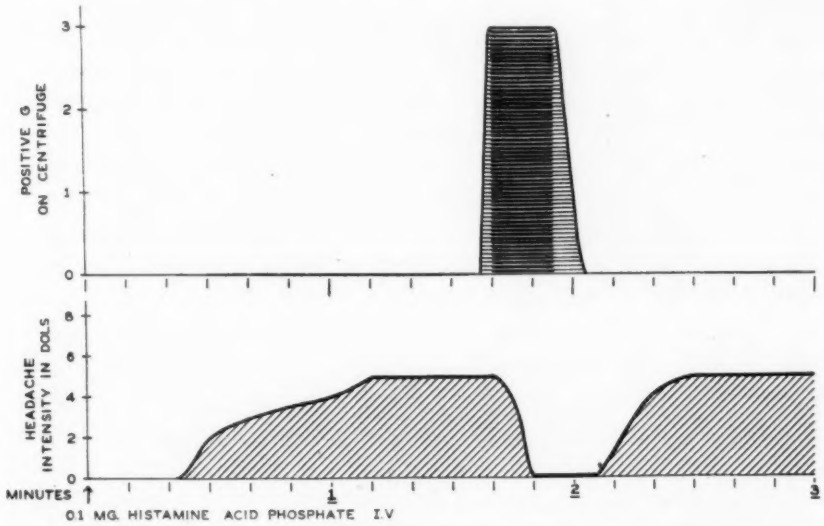

Fig. 3 (male subject, aged 31).—Elimination of vascular headache induced with histamine phosphate during centrifugation at a positive acceleration of 3.0 g.

centrifugation two minutes later, when the headache had spontaneously subsided to 3 dols, the relief from headache was complete.

The caffeine-withdrawal headaches also responded well to centrifugal force. On two separate runs for each subject the pain was completely eliminated during exposure to + 2.0 g and rose to its original intensity within ten seconds after the centrifuge ceased to turn. The results of one such experiment are shown in figure 4 *A*.

Comment.—The thesis that headache arising from distention of cranial arteries might respond to increased positive g is here confirmed. The elimination of the headaches was striking and coincided with the peak effect of the induced forces. It seems evident also that positive

21. Dreisbach, R. H., and Pfeiffer, C.: Caffeine-Withdrawal Headache, J. Lab. & Clin. Med. **28**:1212, 1943.

g as low as 2.0 can suffice to produce the effect, provided the intensity of the headache (presumably a measure of the degree of arterial distention) is not unduly high. The assumption that histamine headache is of vascular origin rests on convincing studies by past investigators, but the inclusion of caffeine-withdrawal headache in this category may need justification. Evidence adduced by others suggests that such headache stems from the sudden withholding of a substance which is both a diuretic and a vasoconstrictor.[21] The temporary increase in blood volume and the relaxation of cranial arteries which are thought to ensue are probably the principal factors in the headache. Whether the pain arises mainly from the branches of the internal or the external carotid artery has not been established; both systems may contribute.

C. Clinical Vascular Headaches.—In addition to the headaches experimentally induced, headaches arising from other causes, i. e., of "clinical" type, were studied in 6 subjects. In all, the pain was predominantly frontal or frontotemporal in location. As will be stated in detail under the case reports, the history and responses of the headaches to certain manipulations indicated that these pains were of vascular origin. In the instructions given the subjects prior to the experiments in the centrifuge, particular care was taken to avoid the effects of suggestion regarding the results to be anticipated.

In every instance the headache was completely eliminated during, and for a few seconds after, exposure to + 2.0 g for periods of ten to twenty seconds. The series comprised a case of headache apparently precipitated by omission of breakfast in a subject known to have had such "hunger" headache repeatedly in the past, a case of headache following a moderate concussion sixteen hours before and 4 instances of headache related to emotional tension.

CASE 1.—*"Hunger" headache in an Army medical officer aged 36.*

For many years the physician had noted the occurrence of mild or moderately severe dull bifrontal headache if he omitted a meal, particularly if it was breakfast. Experience had demonstrated that omission of coffee was not the determining factor. Similar headache was also occasionally noted during periods of tension.

The headache available for acceleration studies began at 11: 30 a. m. on a day on which he had abstained from breakfast. The pain reached moderate intensity (3 dols) one hour later and, despite lunch at 12: 45 p. m., rose to 4 dols by mid-afternoon. It was noted that the headache was easily made worse by mild head shaking and that it was slightly accentuated by brief or prolonged straining, evidence favoring intracranial arteries, and perhaps also extracranial arteries, as the source of the pain.

During centrifugation at + 2.0 g for fifteen seconds in two separate tests three hours apart, the headache was completely eliminated, returning to its original level within fifteen seconds after the centrifuge had stopped. The results of the second trial are diagrammed in figure 4 *B*. The headache cleared spontaneously in midevening.

CASE 2.—*Acute "postconcussion" headache in a woman aged 27, a secretary.*

Early in the night prior to the day of observation the patient was severely stunned by a blow to the occiput, when she fell while ice skating. She was briefly confused but did not lose consciousness. Pain at the site of the blow was moderate. The following morning she noted mild tenderness over the area of occipital contusion and moderate bitemporal headache, made worse by sudden movement of the head. Her headache was readily accentuated by brief straining and was abolished during straining maintained for ten seconds. It was inferred that the pain arose primarily from distention of intracranial arteries.

During each of two exposures to acceleration of + 2.0 g for fifteen seconds her headache was completely abolished; it returned slowly during the two minutes after each test run. The headache was gone on the following day.

CASE 3.—*"Emotional tension" headache in an Army private, aged 27, an aviation mechanic.*

For five years the patient had noted frequent bifrontal headaches, often associated with nasal congestion, nausea and lethargy. It had been assumed for

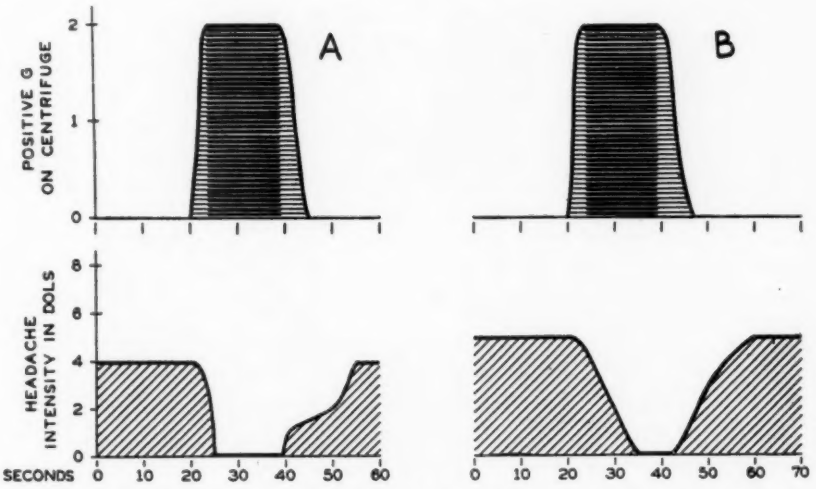

Fig. 4.—Elimination of experimental and clinical headaches of vascular origin during centrifugation at a positive acceleration of 2.0 g: *A* (male subject, aged 27), headache induced by the abrupt suspension of caffeine after administration of the drug for nine days; *B* (male subject, aged 36), headache noted four to eight hours after omission of breakfast in a subject prone to such "hunger" headache.

some time that the headache was of sinus origin, although the pain sometimes occurred during periods of freedom from nasal complaints and in relation to tension-producing circumstances. He was referred for study because of a typical attack of headache beginning four days before. The symptom began in a setting of considerable tension, for on the day of onset he was abruptly relieved of his regular duties and assigned to what he considered a menial job, assisting in the construction of an exhibit. Because he had derived pride and satisfaction from his special skills as a mechanic, he found the new arrangement unacceptable. He suspected, moreover, that it might lead to permanent malassignment. His dominant feelings in this situation were those of resentment and anxiety.

At the time he was examined the headache was mild (2 dols). Its intensity was easily increased by mild head shaking and was greatly diminished by

sustained straining, evidence suggesting, as in case 2, that the headache arose mainly from dilated intracranial arteries. The nasal mucosa was moderately reddened and congested, and there was a scanty, thin, watery discharge. He had no fever. Roentgenograms of the paranasal sinuses showed an essentially normal condition.

Centrifugation at an acceleration of + 2.0 g for ten seconds, and a few minutes later for twenty seconds, led to complete cessation of the headache during the periods of peak g. The pain returned promptly after each run was finished. On the day after the experimental studies he sustained an injury to one hand while at work and, with this disability, remained free of headache for the next five days.

CASE 4.—*"Emotional tension" headache in a dental technician, aged 22, a corporal in the WAC.*

For four weeks the patient had noted almost daily headaches of moderate severity, either in the right frontal region or generalized, and unaccompanied with visual symptoms or nausea. Ergotamine tartrate administered intramuscularly on four occasions had given partial relief. The onset of her illness

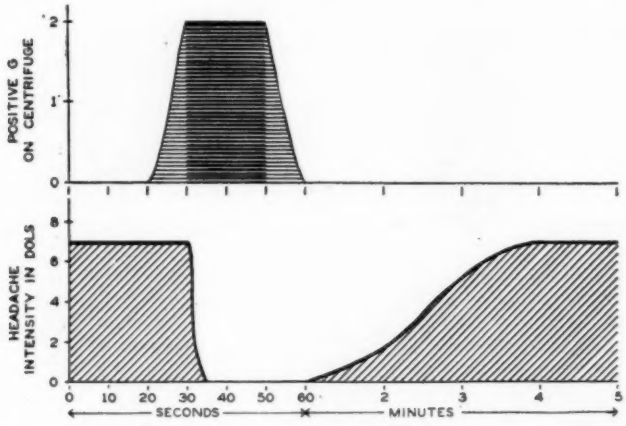

Fig. 5 (female subject, aged 22).—Elimination of atypical migraine headache, developing under work tension, during centrifugation at a positive acceleration of 2.0 g.

could be related to increasing stress in her daily work routine. Because of a reduction in the number of assistants in the dental clinic, she had recently been forced to assume new and time-consuming duties. In the face of these new responsibilities she became tense and dissatisfied, but had no opportunity to ventilate her resentments. The primary tension in this patient centered about her inability to maintain her usual high standards of performance.

On the day of study, her generalized headache, of 7 dol intensity, was not altered by moderately vigorous head shaking or by straining, an observation suggesting that the vascular components in the pain were extracranial, as in migraine, to which this illness seemed related. Her blood pressure was well within normal limits.

The initial centrifugation, at a positive acceleration of 2.0 g for ten seconds, induced a moderate decrease in the intensity of her headache. For this novice on the centrifuge, the first experiment was accompanied with considerable apprehension and bodily tension, which may have accounted for the incomplete relief of the headache. On a second run, for twenty seconds, a few minutes later,

during which she felt fairly well relaxed, the headache cleared completely as soon as peak in g was reached and returned slowly after the cab came to rest (fig. 5). A third trial, with a positive acceleration of 2.0 g for ten seconds, likewise temporarily abolished the headache.

The sequence of events in the three trials argues strongly that distraction played no significant part in the improvement of this patient's headache under increased positive g, for if distraction were responsible the reduction in the pain should have been maximal on the initial run, the exposure which she found most disconcerting. It is probable that her manifest apprehension and inadequate relaxation on the first trial tended to offset in part the usual action of increased positive g on the circulation, just as conscious straining by the aircraft pilot in a tight turn effectively increases his g tolerance.

CASE 5.—*"Emotional tension" headache in a man aged 29, a physiologist.*

Since childhood the patient had experienced occasional hemicrania of mild or moderate intensity, located in the right frontotemporal area and rarely extending back to the right side of the occiput. Such headache sometimes followed prolonged reading but could not be related by the patient to any other situation. It was readily augmented by sudden movement of the head, by bending over or by straining or coughing. The headache available for study had been present part of each day for two weeks in a setting of moderate tension. The clinical features suggested that the pain was of vascular origin, arising from intracranial, and possibly from extracranial, arteries.

During exposure to a positive acceleration of 2.0 g for fifteen seconds, his headache, 3 dols in intensity, was entirely eliminated. The pain returned gradually with deceleration of the centrifuge, transiently rose to about 4 dols as the cab halted and then fell to its former level. The patient observed that during the run at peak g head shaking of moderate force elicited no headache, whereas jolts of similar force before the run regularly induced transient increases in the hemicrania.

CASE 6.—*"Emotional tension" headache in a male physician aged 31.*

For approximately ten years the subject had experienced infrequent and brief episodes of mild bifrontotemporal headache, accompanied with feelings of tightness in the posterior muscles of the neck, when under stress in certain tension-producing circumstances. The stresses most prone to evoke these symptoms were those associated with strong resentment, indecision or fear of failure in a vital assignment. A headache of this type developed on a morning on which the need arose for a decision of critical importance in an experimental program. Owing to circumstances beyond his control, the success of the project was threatened, and no wholly satisfactory solution was evident. The headache elicited in this setting of frustation lasted until a definite course of action was agreed on and set in operation later in the day. His headache was mild (1 dol in intensity) and was essentially unaffected by moderately vigorous head shaking or by straining. The clinical data in this case offered no direct evidence concerning the source of the pain except to suggest that intracranial arteries were not primarily implicated. The nuchal tautness undoubtedly was a manifestation of sustained muscular tension in the posterior neck muscles.[23] It is postulated that the frontotemporal headache arose from distention of cranial arteries.

22. Footnote deleted.

23. Simons, D. J.; Day, E.; Goodell, H., and Wolff, H. G.: Experimental Studies on Headache: Muscles of the Scalp and Neck as Sources of Pain, A. Research Nerv. & Ment. Dis., Proc. **23**:228, 1943.

Centrifugation at a positive acceleration of 2.0 g for fifteen seconds induced complete elimination of the headache, beginning as the peak g was reached. The pain returned as the centrifuge stopped.

III. HEADACHE INDUCED BY RELEASE FROM INCREASED POSITIVE G

Methods.—An analysis was made of sensations observed by 3 subjects who had had unusually extensive experience in g studies on the centrifuge and in aircraft. The symptoms reported were correlated with phenomena noted in available records of amplitude and volume of the ear pulse (as measured by a photoelectric cell chamber applied to the pinna of one ear) and in colored motion pictures of various subjects during and immediately after exposure to increased positive acceleration.

Results.—Each of the 3 subjects who were veterans of g experiments had sometimes noted headache for a few seconds during the release phase after a period of increased positive g. Such headache was most likely to occur after exposure to highly positive acceleration in the seated position or after lower acceleration in the supine position. In the subject who seemed most liable to this minor complication, a moderately intense, throbbing bitemporal headache was sometimes noted during the three second period of deceleration after an exposure in the supine position to a positive acceleration of 2.0 g for fifteen seconds. The headache generally reached a maximum as the cab came to a halt and subsided a second later. In experiments in the seated position, the same subject noted no headache after exposure to low acceleration, but in a series of five runs at a positive acceleration of 4.0 g for nine seconds he noted headache similar to that previously described during each deceleration. Similar headache also was usually noted by this subject in airplane experiments during rapid release from highly positive acceleration of 7.0 to 9.0 g for three seconds. These headaches coincided in time with other phenomena typically noted during deceleration: brief flushing of the face and neck, and (in some representative records) a transient increase in the amplitude, and occasionally in the volume, of the ear pulse above the control levels. Such reactive distention of the superficial vessels of the face following blanching during the centrifugation has also been noted by other investigators.[24]

Comment.—These symptoms and signs noted during release from increased positive acceleration are presumably closely related to a "rebound" elevation of pressure in the cranial arteries, which may reach a peak during the deceleration and thus lead to fleeting distention of cranial arteries. The pressor reflexes which act to restore in part the cranial arterial pressure after the first seven seconds at increased positive g tend also to produce a transient hypertension as the

24. Franks, W. R.; Kerr, W. K., and Rose, B.: Some Effects of Centrifugal Force on the Cardio-Vascular System of Man, J. Physiol. **104**:9, 1945.

centrifuge decelerates.[4] It has been shown that a sudden increase in intramural pressure within the cranial arteries, such as that which follows the intravenous administration of epinephrine, can in itself produce headache.[25] In the headache which follows centrifugation, a second factor facilitating distention of the arteries may also be involved. This is a decrease in vasoconstrictor tone in the intracranial vessels secondary to the fall in cranial arterial pressure induced by the increased positive g, with a delayed recovery of normal arterial tone during the release phase.[26]

A somewhat similar situation dependent primarily on a chemical, rather than a mechanical, stimulus exists in the case of headache induced by histamine, for the latter type of headache does not develop until the blood pressure, initially depressed by the systemic effects of the drug, returns to a normal, or briefly hypertensive, level and then distends intracranial arteries still relaxed under the local action of histamine.[6] It is conjectured that an analogous change occurs after exposures to increased positive g and that a decrease in intracranial arterial tone may contribute to the production of a "release" headache (vividly termed "up-surge" headache by a subject familiar with this symptom). It is uncertain whether the pain arises from intracranial or from extracranial arteries or from both.

At this point, it is pertinent to mention that another analogue of "release" headache is to be found in the experience of many pilots. The facial congestion so readily induced during the maneuver of an outside loop in an airplane, or by negative acceleration of 2.0 or 3.0 g on the centrifuge, is frequently accompanied with an intense throbbing headache, which may persist for several hours. That carotid blood pressure is greatly elevated during such negative g stresses has been demonstrated in animal experiments.[5] The branches of the external carotid artery are thus subjected to sudden and severe stretching forces. But whether the divisions of the internal carotid artery are similarly put under stress is yet in doubt, for the pressure of the surrounding cerebrospinal fluid doubtless also rises under negative acceleration, owing both to the hydrostatic pressure of the fluid column and to an elevation in intracranial venous pressure. Hence, some protective support may be offered the intracranial arteries.[26a] Yet pathologic studies of animals subjected to negative acceleration have revealed sustained dilatation and congestion of pial vessels and hemor-

25. Cameron, D. E.: Increased Reactivity caused by Adrenalin, Am. J. Med. Sc. **213**:331, 1947. Wolff and Hardy.[19]

26. Wolff, H. G.: The Cerebral Circulation, Physiol. Rev. **16**:545, 1936.

26a. Hamilton, W. F.; Woodbury, R. A., and Harper, H. T.: Physiologic Relationships Between Intrathoracic, Intraspinal and Arterial Pressures, J. A. M. A. **107**:853 (Sept. 12) 1936.

rhage from small vessels, and perhaps even from the circle of Willis.[5] It may be postulated, therefore, that headache induced by negative acceleration arises from distention of cranial vascular structures, particularly the unprotected vessels on the outside of the head, but perhaps also imperfectly buttressed intracranial vessels.

GENERAL COMMENT

The data have shown that headache arising from painful distention of cranial arteries can be abolished during the application of a controlled mechanical stress, increased positive g. It is inferred that the elimination of such headache is a direct result of the concurrent fall in intravascular pressure at the head level and does not depend on a barrier to pain perception per se. A series of headaches of known vascular origin and others of suspected vascular origin all responded promptly to the centrifuge test. In a few instances the relief obtained outlasted the exposure to increased positive acceleration by one or two minutes. This suggests the possibility that cranial arterial tone may have been favorably altered for a short time by the transient fall in intramural pressure. It can be stated that the human centrifuge has shown value as a diagnostic tool, specifically applicable to the analysis of mechanisms of headache.

The experiments here reported represent only a limited exploration of the uses of a new investigative method. It is conjectured that certain other vascular headaches would also yield to increased positive g, e. g., typical migraine headache (early in an attack [27]); the headaches associated with hypertension, fever or anoxia, and certain headaches persisting long after head trauma.[28] The intensity of headache arising solely from sustained tension in muscles of the head and neck might be little, if at all, reduced by centrifugation.[22] On the other hand, headaches due to traction on (in association with cerebral tumor or following lumbar puncture) or to inflammation of (meningitis) pain-sensitive intracranial structures would probably be intensified; patients in these categories, however, would be ill suited to so vigorous a diagnostic technic.

In this report we have also referred to the probable mechanisms of two mechanically induced headaches for which there apparently are no exact clinical counterparts: the headache occasionally noted during

27. Torda, C., and Wolff, H. G.: Experimental Studies on Headache: Transient Thickening of Walls of Cranial Arteries in Relation to Certain Phenomena of Migraine Headache and Action of Ergotamine Tartrate on Thickened Vessels, Arch. Neurol. & Psychiat. **53**:329 (May) 1945.

28. Simons, D. J., and Wolff, H. G.: Studies on Headache: Mechanisms of Chronic Post-Traumatic Headache, Psychosom. Med. **8**:227, 1946. Friedman, A. P., and Brenner, C.: Post-Traumatic and Histamine Headache, Arch. Neurol. & Psychiat. **52**:126 (Aug.) 1944.

release from increased positive g, and the headache which is a prominent feature of exposure to negative g. Both varieties demonstrate anew the importance of distention of cranial vessels in the genesis of headache.

SUMMARY

Exposure to a positive acceleration of 3.0 or 4.0 g (centrifugal forces in the head to seat direction) on the human centrifuge had little or no effect on the pain threshold to the stimulus of radiant heat or on the intensity of pain induced by a variety of stimuli.

Experimentally induced headaches of nonvascular origin arising from compression or irritation of the surface tissues of the head were only slightly reduced in intensity during exposure to a positive acceleration of 3.0 g; the minor changes in such headaches were attributable to distraction.

Experimentally induced headaches of moderate severity arising from distention of cranial arteries (histamine and caffeine-withdrawal headaches) were eliminated during exposure to positive accelerations of 2.0 or 3.0 g, a relief attributable to a concurrent fall in intravascular pressure at the head level.

Clinical headaches of vascular origin responded similarly, for in subjects experiencing headache related to hunger, recent head trauma or emotional tension, all with clinical features suggesting that the pain arose from distention of intracranial or extracranial arteries, the headache was completely eliminated during exposure to a positive acceleration of 2.0 g.

A brief headache was sometimes noted in the normal subject during release from increased positive g; such headache probably arises from transient distention of cranial arteries, and in this respect is the analogue of headache induced by negative g.

The human centrifuge is a useful tool in the analysis of vascular mechanisms in headache.

Capt. William Koerschner, United States Air Force, gave technical assistance in the experiments, and Miss Helen Goodell aided in preparation of the illustrations.

Duke University School of Medicine, Durham, N. C.

BAL THERAPY OF SEVERE PERIPHERAL NEUROPATHIES

A. R. FURMANSKI, M.D.

Chief of Neurology Section, Neuropsychiatric Service, Birmingham Veterans Administration Hospital
VAN NUYS, CALIF.

IT IS the opinion of some neurologists that the neuropathies are initially biochemical disorders of the neuron, due chiefly to disruption of one or more enzyme systems that regulate the metabolism of the cell. According to this theory, the neuronal dysfunction that results can be severe but structural changes in the myelin or axon need not occur. Neurons in this stage of dysfunction should be able to recover rapidly over a period of hours or days if enzymatic equilibrium is restored. Anesthetics, such as procaine, are capable of producing analogous dysfunction and rapid recovery. Such rapid resolution of impaired conduction is inconsistent with recovery from structural changes in the neuron, which proceeds at a rate of from 0.5 to 2 mm. a day. When the disruption of cellular metabolism has reached an irreversible stage, degeneration of the neuron results, and recovery will follow the laws of regeneration.

Dr. J. M. Nielsen, senior consultant in neurology to this hospital, suggested that the attack on neuropathies be made by attempting to restore enzymatic equilibrium with the substance that had demonstrated such capabilities in the heavy metal intoxications, namely, the dithiol 2,3-dimercaptopropanol. This synthetic derivative of propanol, containing two sulfhydryl radicals, was introduced under the name "British anti-lewisite," abbreviated to the more familiar BAL.[1] It had successfully restored enzymatic equilibrium in the intoxications with arsenic,[1] mercury,[2] antimony[3] and cadmium.[4]

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1. (*a*) Peters, R. A.; Stocken, L. A., and Thompson, R. H. S.: British Anti-Lewisite (BAL), Nature, London **156**:616 (Nov. 24) 1945. (*b*) Waters, L. L., and Stock, C.: BAL (British Anti-Lewisite), Science **102**:601 (Dec. 14) 1945.

2. Longcope, W. T., and Luetscher, J. A.: The Treatment of Acute Mercury Poisoning by BAL, J. Clin. Investigation **25**:557 (July) 1946. Gilman, A.; Allen, R.; Philips, F. S., and St. John, E.: The Treatment of Acute Systemic Mercury Poisoning in Experimental Animals with BAL, Thiosorbital and BAL Glucoside, ibid. **25**:549 (July) 1946.

In recent months the opportunity to use BAL in 4 cases of severe neuropathy was utilized to study this problem. In these cases there was no question of heavy metal intoxication. The etiologic factors were primarily infectious or metabolic. The response to BAL was striking enough to merit this preliminary report.

To consider the possible action of BAL in neuropathies, one must understand the mechanism of heavy metal intoxication and the action of BAL in cases of such poisoning. It is well established that heavy metals have an affinity for the sulfhydryl radical in organic and inorganic molecules.[5] In the heavy metal intoxications, the metal combines with the sulfhydryl component of the cellular proteins. Among the proteins in the cell that contain sulfhydryl radicals are essential enzymes regulating carbohydrate and fat metabolism. Such enzymes owe their activity to the sulfhydryl radical. When these enzymes are inactivated by the heavy metals, cellular respiration is greatly impaired.[6]

The solution to the problem was found in the fact that certain thiols, such as cysteine and glutathione, had a greater affinity for the metals than the cellular thiol. The dithiols surpassed the thiols in this capacity.[7] The best of the dithiols, BAL, was found capable of removing the metal from the enzyme protein by forming a more stable ring compound, which was insoluble and nontoxic and was excreted rapidly from the body. Unfortunately, some metals, such as lead, when conjugated with BAL form substances almost as toxic as the metals themselves.[8]

This affinity of BAL for metals also accounts for some of its toxic properties. Many enzymes possess metals, such as copper, zinc, iron and magnesium, as essential prosthetic groups. Dithiols can also remove these metals from the cell, thus inhibiting the enzyme systems so deprived of their prosthetic group. Evidently, this occurs only with large doses of BAL. The inhibition can be reversed by supplying the deficient metal.[9]

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3. Eagle, H.; Germuth, F. G.; Magnuson, H. J., and Fleishman, R.: Protective Action of BAL in Experimental Antimony Poisoning, J. Pharmacol. & Exper. Therap. **89**:196 (Feb.) 1947.

4. Simon, F. P.; Potts, A. M., and Gerard, R. W.: Action of Cadmium and Thiols on Tissues and Enzymes, Arch. Biochem. **12**:283 (Feb.) 1947.

5. Eagle, H.; Magnuson, H. J., and Fleishman, R.: The Systemic Treatment of Experimental Arsenic Poisoning (Mapharsen, Lewisite, Phenyl Arsenoxide) with BAL, J. Clin. Investigation **25**:451 (July) 1946.

6. Barron, E. S.; Miller, Z. B.; Bartlett, G. B.; Meyer, J., and Singer, T. P.: Reactivation by Dithiols of Enzymes Inhibited by Lewisite, Biochem. J. **41**:69 (Jan.) 1947. Waters and Stock.[1a]

7. Footnote 1. Eagle and others.[5]

8. Germuth, F. G., and Eagle, H.: The Efficacy of BAL (2,3-Dimercaptopropanol) in the Treatment of Experimental Lead Poisoning in Rabbits, J. Pharmacol. & Exper. Therap. **92**:397 (April) 1948.

(Footnotes continued on next page)

The usual regimen of therapy for severe neuropathies at this hospital had consisted of high vitamin diets, use of crude liver extract and administration of vitamins in crude and refined forms, orally and parenterally. In the cases presented in this paper, the neuropathy was little affected by such therapy, the disease in 2 of the cases continuing to progress to severe motor and sensory deficit.

The BAL used in the cases of this report consisted of a 10 per cent solution of 2,3-dimercaptopropanol with 20 per cent benzyl benzoate and peanut oil as the vehicle. The injections were given once daily for periods of nine to twenty-two days. The total amount of BAL given ranged from 0.89 to 2.86 Gm.

REPORT OF CASES

CASE 1.—A white man aged 68 dated his illness to October 1947; at this time he felt run down and had a chest cold, which had persisted about six weeks, up to the time of his admission to the hospital. He had eaten poorly, vomited daily and had diarrhea during the last half of this period. The past history revealed that the patient had had a posterior gastroenterostomy in 1944 for a peptic ulcer and since then had had intermittent bouts of diarrhea.

On admission to the veterans' hospital on Dec. 6, 1947, his temperature was 100 F., and he was dehydrated and had a swollen, slick, beefy red tongue. He was disoriented and confused and showed bilateral pneumonitis clinically and roentgenologically. The sedimentation rate was 41 mm. per hour and the erythrocyte count 3,650,000. The leukocytes numbered 10,150 with 70 per cent neutrophils. The nonprotein nitrogen of the blood was 50 mg. per hundred cubic centimeters. He was given penicillin, 50,000 units every three hours, and 5 cc. of a soluble preparation of vitamin B (solu B R)[10] daily. The penicillin was discontinued after eight days, the patient having become afebrile and mentally clear and the pneumonitis having resolved. The nonprotein nitrogen of the blood was 27.6 mg. per hundred cubic centimeters on December 11.

The anemia noted on his admission persisted, the erythrocytes averaging 3,200,000, the color index 1 and the hematocrit reading 30. On December 13, the blood smear showed many target cells and some macrocytosis and anisocytosis. Gastric analysis on December 15 showed 10 units of free hydrochloric acid in the fasting sample and 40 units after injection of histamine. Ferrous sulfate was begun on December 18, 15 grains (0.975 Gm.) being given daily.

In the middle of December the patient began to complain of tingling and weakness in his hands and feet. He had been receiving 5 cc. of soluble vitamin B preparation intramuscularly daily since admission. Neurologic examination showed

9. Barron and others.[6] Barron, E. S.; Miller, Z. B., and Meyer, J.: The Effect of 2,3-Dimercaptopropanol on the Activity of Enzymes and on the Metabolism of Tissues, Biochem. J. **41**:78 (Jan.) 1947. Webb, E. C., and Van Heyningen, R.: The Action of British Anti-Lewisite (BAL) on Enzyme System, ibid. **41**:74, (Jan.) 1947.

10. This preparation contains 10 mg. of thiamine hydrochloride, 10 mg. of riboflavin, 5 mg. of pyridoxine hydrochloride, 50 mg. of calcium pantothenate and 250 mg. of nicotinamide in powder form for injection after proper solution has been effected.

hyperactivity of the deep reflexes and absence of position and vibration senses in both lower extremities. His anemia had shown no response to the iron therapy. On December 29 the erythrocytes numbered 3,160,000; the hemoglobin measured 12 Gm. per hundred cubic centimeters; the color index was 1.2 and the hematocrit reading 35. The spinal fluid, examined on December 29, was entirely normal. Crude liver extract (2 U. S. P. units per cubic centimeer) was begun on December 30, 5 cc. being given twice a week.

During January the weakness and tingling progressed, so that on January 16 he was unable to stand because of weakness in the legs. At that time vibration sense was absent in both upper and lower extremities, the deep reflexes were hypoactive and the hands weak. Liver therapy was discontinued on January 20. The blood findings on January 29 were as follows: erythrocytes, 4,190,000; hemoglobin, 12.5 Gm. per hundred cubic centimeters; color index, 0.9; hematocrit reading, 41, and reticulocyte count, 0.7 per cent. The highest reticulocyte count during the month of liver extract therapy was 1.2 per cent. "Reticulogen" (a preparation containing the antipernicious anemia principle), folic acid (pteroyl glutamic acid) and brewers' yeast were tried during the next week, without any effect on the anemia or the neuropathy. On February 10 the erythrocyte count was 3,700,000 and the hemoglobin content 11.75 Gm. per hundred cubic centimeters.

On February 11 the neurologic examination showed pronounced weakness of the toes, moderate weakness of movement of the ankles and fingers and mild weakness of movements of the knee, hip and wrist bilaterally. The interosseus muscles were paralyzed and atrophic. Appreciation of pain was diminished from the knees and wrists distally. Touch perception was impaired over the foot, toes, hands and fingers. Vibration could not be felt up to the thoracic cage or in the fingers or wrists. Position sense was absent in the lower extremities and diminished in the fingers. The deep reflexes could not be elicited. The patient had been receiving 5 cc. of the soluble vitamin B preparation and 1½ ounces (46.6 Gm.) of brewers' yeast daily during this period of progression of the neuropathy.

By February 17, vibration sense was absent up to the clavicle, and appreciation of touch and pain senses was defective from the elbow and hips distally. The weakness had increased, the proximal muscle groups becoming very weak and the distal groups paralyzed.

On February 17, injections of BAL, 160 mg. (2.5 mg. per kilogram of body weight), and 5 cc. of crude liver extract (10 U. S. P. units) were begun intramuscularly once a day. The progression of the neuropathy ceased and in the subsequent few days improvement began. By February 28 strength had returned to all muscle groups, so that movement against gravity was possible, even in the toes. The biceps reflexes were present. BAL was discontinued on March 4, and the dose of liver extract was reduced to 5 cc. (10 U. S. P. units) twice a week. Vitamin therapy was continued in smaller doses. By April 1 the patient was walking about; and strength against resistance had returned to all muscle groups, but was not equal to the preillness level. The deep reflexes were present, and no sensory loss was demonstrable objectively. The total amount of BAL given was 2.72 Gm., over a period of seventeen days.

Case 2.—A white man aged 29 began in 1945 to have morning nausea and vomiting, restlessness, tension and insomnia. In the summer of 1947 his food intake became faulty, owing to lack of appetite. To allay his "nervousness," he resorted to the sedative action of several highballs daily. In November 1947 he noted a "sleeping" sensation in the right big toe; this sensation spread to the other toes within a few days. The paresthesia was constant and was par-

ticularly evident in the evenings and mornings. The same progression of sensory disturbances occurred in the left foot. Gradually, over a period of several weeks, numbness, stiffness and cramping spread upward to the lower third of each thigh. In January a burning sensation, together with redness and a feeling of heat, was noted in the feet. The muscles of the legs felt stiff, and the patient had much trouble in walking.

He entered the veterans' hospital on December 26. At that time he showed a wide-based gait, a positive Romberg sign, mild weakness of the lower extremities, moderate ataxia in the heel to knee tests, diminished appreciation of pain and touch sense below the lower third of the thighs, absence of vibration sense below the pelvis, tenderness of the nerve trunks in the legs, dysesthesias over the soles, exaggerated deep reflexes in the lower extremities, signs of involvement of the pyramidal tract bilaterally and hyperhidrosis and flushing below the midcalf region in a stocking pattern. Paresthesias were present below the knees and in the the finger tips.

The laboratory studies on his admission showed 4,960,000 erythrocytes, 15.25 Gm. of hemoglobin per hundred cubic centimeters and 6,000 leukocytes, with 12 monocytes per hundred cells. On January 27 the spinal fluid was normal except for 50 mg. of total protein per hundred cubic centimeters. Cephalin flocculation, thymol turbidity and sulfobromophthalein tests all indicated normal hepatic function. Gastric analysis showed 60 units of free hydrochloric acid in the fasting sample and 100 units after injection of histamine. Treatment was started with twice the daily requirement of vitamins and 20 mg. of thiamine hydrochloride daily.

No change occurred under this vitamin regimen. On February 5, 1 cc. of the soluble vitamin B preparation given intramuscularly three times a week and ½ ounce (15 Gm.) of brewers' yeast daily were added, without any effect. On February 11 crude liver extract, in doses of 5 cc. (10 U.S.P. units), was begun and was given intramuscularly daily for ten days. Repeated blood counts were taken during this period, the erythrocyte count varying from 4,120,000 to 4,700,000, with moderate anisocytosis and poikilocytosis. The highest reticulocyte count was 1 per cent. The bone marrow, examined on February 18, was normal. The high monocyte count (12 per cent) noted on admission persisted, counts of 14, 11, 16 and 9 per cent being made. Because of urgent business reasons, the patient had to leave the hospital on February 25. There had been a slight improvement in his gait during his stay in the hospital. He was given brewers' yeast and multivitamins to take while away from the hospital.

He returned to the hospital on April 6, essentially in the same state as he had left it. His gait still was extremely ataxic, so that he fell and sprained his ankle on the first day back. On April 8 BAL therapy was begun, 200 mg. (3 mg. per kilogram) being given daily for two days and then 70 mg. (1 mg. per kilogram) daily. In addition he received 5 cc. of crude liver extract daily and 1 ounce (30 Gm.) of brewers' yeast three times a day. The symptoms and signs disappeared so rapidly that after nine days the BAL and liver were discontinued. He was discharged on April 19, essentially well. Only mild weakness and brisk deep reflexes remained of the previous severe motor and sensory neuropathy and pyramidal tract deficit that had existed eleven days before. The total amount of BAL given was 0.89 Gm., in a period of nine days.

Case 3.—A white woman aged 58 had never regained her full strength since having pulmonary tuberculosis with effusion in 1919, although the process had been healed since 1921. Her main disability was chronic fatigability. In 1946

this fatigability increased, and her erythrocyte count was found to be 2,000,000. She received liver and iron therapy from July 1946 to September 1947. In September 1947 her hemoglobin measured 89 per cent, and the fatigability was alleviated. Liver was discontinued in September 1947, but the iron therapy was continued.

In May 1948, after heavy exertion, she experienced pains in the back, which radiated around to the front along the lower costal margin. Sometimes it felt as though a band were compressing the chest. About May 24 she noted fever, became dizzy and nauseated and had diarrhea. She entered another hospital for these disorders on May 27. Her erythrocyte count at that time was 1,890,000; the hemoglobin concentration, 28 per cent, and the leukocyte count, 11,300. She was given a transfusion of 500 cc. of whole blood, and treatment with large doses of vitamins was started. The erythrocyte count on June 1 was 2,500,000 and the hemoglobin concentration 46 per cent. The blood smear showed hypochromia, microcytosis, poikilocytosis and absence of reticulocytes. Treatment with crude liver extract was begun on June 1, 1 cc. being given intramuscularly daily. On June 4 the erythrocyte count was 2,650,000; the hemoglobin concentration, 57 per cent, and the reticulocyte count, 10 per cent. Gastric analysis showed no free acid in the fasting specimen and 15 units of free hydrochloric acid after injection of histamine. She was transferred to the Birmingham Veterans Administration Hospital on June 10.

On entry to the hospital, analysis of the gastric secretion showed no free acid in the fasting specimen and 20 units of free hydrochloric acid after injection of histamine. The blood count showed 2,590,000 erythrocytes, a hemoglobin content of 9 Gm. per hundred cubic centimeters, a hematocrit reading of 30, moderate anisocytosis with macrocytosis and slight poikilocytosis. She continued to receive 1 cc. of crude liver extract and vitamins daily. The cephalin flocculation and thymol turbidity tests revealed normal hepatic function. The bone marrow on June 16 showed active erythropoiesis, primarily normoblastic, and was reported as essentially normal. The peripheral blood was interpreted as showing normochromic normocytic anemia, the erythrocytes numbering 4,060,000, the hemoglobin measuring 12.5 Gm., the hematocrit reading being 41 and the reticulocyte count 0.8 per cent.

On June 21 she again began to complain of pain between the shoulder blades and to have nausea and vomiting. She continued to vomit intermittently for four days. On June 25 she complained of numbness and extreme weakness of the extremities. There were no objective neurologic signs other than moderate weakness. By June 28 the numbness and weakness extended from the face to the toes. Neurologic examination on June 28 showed complete paralysis of the lower extremities and extreme weakness of the upper extremities. The muscles and nerves were tender to palpation. Vibration sense was absent in the lower extremities. The skin below the knees was dysesthetic. The deep reflexes were absent and the Kernig sign was positive. Mild nuchal rigidity was present. The right side of the palate, the right pterygoid muscle and the muscles of the right side of the face were paretic. Examination of the spinal fluid revealed no cells, 131 mg. of total protein, 605 mg. of chlorides and 92 mg. of sugar per hundred cubic centimeters and a Lange (colloidal gold) curve of 000132100. The erythrocyte count at this time, June 28, was 4,470,000 and the hemoglobin content 13.74 Gm. per hundred cubic centimeters. On July 2 the neurologic findings had not changed.

On July 3, BAL therapy was begun, 100 mg. (1.5 mg. per kilogram of body weight) being given daily. The patient continued to take the multivitamins and

the 1 cc. of crude liver extract that she had been receiving since June 1. On the second day of BAL therapy she noted pronounced improvement in the strength of her upper extremities. By July 6 she could move her legs and toes, and the palsies of the cranial nerves had disappeared. Roentgenograms of the spine and the gastrointestinal tract revealed no abnormality. On July 15 she could move the limbs about freely and showed fair power against resistance, except in the fingers. The biceps reflexes had returned. Deep and superficial sensation was intact except for paresthesias and dysesthesias in the fingers and the feet. BAL therapy was discontinued on July 21 and the dose of liver extract was changed to 5 cc. twice a week. The erythrocyte count on July 20 was 4,560,000 and the hemoglobin content 14 Gm. per hundred cubic centimeters. Neurologic examination on July 22 showed continued improvement in motor power and the presence of hypoactive deep reflexes. She had received a total of 1.9 Gm. of BAL over a period of nineteen days.

Case 4.—A white man aged 27 was in good physical health until about April 25, when he had onset of sore throat, fever and malaise. In the next few days there occurred pronounced swelling of the throat and membrane formation on the pharynx, extending up beyond the palate. The patient was admitted to another hospital. Two cultures were negative for diphtheria bacilli. The swelling of the throat was incised, but no pus was obtained. Penicillin and a sulfonamide drug were given for two weeks, until an urticarial eruption developed. The penicillin was discontinued, and the urticaria subsided the next day. The sulfonamide drug was continued for another one and a half weeks. The patient was discharged from the hospital on May 17, asymptomatic.

On May 20 he noted a nasal twang in his voice and his jaws began to ache. Food felt as though it was sticking in his throat. About May 21 the calves began to ache and the skin over the calves and buttocks became very sensitive and remained so for the next few days. They then became numb and tingling and lost much of their sensitivity. About June 5 the legs became weak and unsteady. On June 6 the numbness and tingling became evident in the fingers. By June 7 he had to resort to the use of canes to walk.

He was admitted to this hospital on June 10. He could then walk with support. There was only mild muscular weakness in the legs, and strength in the upper limbs was normal. The heel to knee tests showed moderate ataxia. Position sense was diminished and vibration sense absent in the legs. Hypalgesia was noted in a stocking pattern below the knees, but touch was intact. Dysesthesias were manifested over the soles. Superficial and deep sensation was normal in the hands, but two point discrimination and stereognosis were defective. The hands and fingers were subjectively numb and tingling, as were the lower limbs below the knees. All the deep reflexes were absent. A definite nasal twang in the voice was present, but no objective palatal weakness was demonstrable.

Laboratory studies on his admission showed an old tuberculous complex in the chest, as seen in the roentgenogram; 6,950 leukocytes, with 55 per cent neutrophils, 31 per cent lymphocytes, 9 per cent monocytes and 5 per cent eosinophils; a sedimentation rate of 42 mm. per hour, and a 3 plus reaction for albumin in the urine.

He was given brewers' yeast, 1½ ounces daily for one week. During this period he began to note weakness in his fingers. On June 18 crude liver extract was begun, 5 cc. being given intramuscularly three times a week. On June 22 the spinal fluid contained 2 lymphocytes per cubic millimeter and 890 mg. of total protein per hundred cubic centimeters and gave a strong Pandy reaction

for globulin. By June 25, the weakness in his fingers was extreme, and the upper portions of the arms were becoming weak as well. In the next few days there was rapid progression of weakness to complete paralysis in the lower extremities and to severe weakness of the proximal arm muscles and paralysis of the distal arm muscles. He lost the appreciation of vibration below the neck and of position in the distal segments of the extremities. Superficial sensation was diminished from the shoulders and hips distally. He had continued to receive the liver and yeast therapy during this period of progression of the neuropathy.

On July 2 BAL therapy was begun, 130 mg. (1.5 mg per kilogram) being given daily. There was prompt cessation of progression of the symptoms, and in the next several days power began to return to the proximal segments of the limbs. After two weeks of BAL therapy, power against resistance had returned to the limbs except in the ankles, toes and fingers. Vibration sense was still absent in the limbs but was present in the trunk. Position sense was absent in the toes and fingers. Pinprick could be appreciated everywhere, although its perception was diminished in the distal segments of the limbs. The deep reflexes were still absent. On July 23 the neurologic status was essentially unchanged and BAL treatment was discontinued. The patient had received 2.86 Gm. of the drug in twenty-two days.

COMMENT

It is apparent that these patients did not respond to large doses of crude liver extract and vitamins. In fact, in 3 of the cases the intake of these substances did not prevent the neuropathies from developing or progressing. Failure of this therapy strongly suggests that the neuronal dysfunction in these cases was due not to a deficiency state but, rather, to inability of the cell to utilize the materials that were present in adequate quantities. That this cellular dysfunction was biochemical, and not structural, is evident in the rapid resolution of the dysfunction, a change not compatible with the known rates of regeneration of the neuron. The fact that this change was initiated by the addition of BAL, a substance known to act on enzyme systems, is also indicative that the early changes in neuropathy are reversible biochemical disorders, as illustrated strikingly in cases 1 and 3.

There is also an indication that cellular dysfunction may exist for many months without structural change and that restoration of the biochemical equilibrium may also result in rapid improvement, as occurred in case 2. Restoration of function in cells where the neuropathy has proceeded to structural change will have to follow the laws of regeneration, and only cells in the reversible stage of dysfunction will benefit by administration of BAL. This is probably the reason for the incomplete response to the drug in case 4.

The mode of action of BAL in these cases may be similar to that of the heavy metal intoxications, i. e., conjugation of a toxin or toxic metabolite which had inactivated the enzyme systems. It is also possible that in the cases of infectious origin BAL inhibits one of the essential enzyme systems of the virus and aids the cell in overcoming

the invasion. Biochemistry will eventually give the answer to this problem.

The therapeutic effects of BAL on the metal intoxications can be secured from doses of 1.5 mg. per kilogram of body weight, amounts well within the nontoxic range of the drug. Clinically, the toxic effects appear in doses of 5 mg. per kilogram of body weight or higher.[11] In 2 of the cases reported here the dose was 3 mg. per kilogram of body weight and in the other 2, 1.5 mg. per kilogram. One patient (case 2) when receiving 3 mg. per kilogram of body weight complained of moderate dizziness, and the dose was reduced to 1 mg. per kilogram of body weight. Another patient (case 4), receiving 1.5 mg. per kilogram, experienced aching and a feeling of heat in the limb where the injection was made, but these symptoms disappeared in an hour. All the patients had mild tenderness and burning at the site of the injection, but no more than that from an injection of liver extract.

When the dose of BAL is 5 mg. per kilogram of weight or higher, the following reactions have been described; conceivably, they might appear after smaller doses if an idiosyncrasy were present: pains and paresthesias in various parts of the body, perspiration and a feeling of warmth, lacrimation, salivation, blepharospasm, tremulousness, nausea, vomiting, restlessness, apprehension, severe malaise and generalized weakness. These reactions lasted only from one to two hours.[11]

SUMMARY

The theory is proposed that initially neuropathies are reversible biochemical disorders of the neuron and that no structural changes of degeneration occur.

The dithiol 2,3-dimercaptopropanol (BAL) has the ability to restore disrupted cellular metabolism by its action on enzyme systems.

Four cases of infectious and metabolic neuropathies are reported. These cases did not respond to therapy with vitamin or crude liver extract. The addition of BAL to the treatment resulted in rapid recovery in 3 cases and in improvement in 1 case.

The rapidity of response and the initiation of the response by BAL indicate that the fundamental process in these cases was a reversible biochemical disorder of the neuron.

The staff of the Birmingham Veterans Administration Hospital, especially Dr. S. C. Bonar, Dr. W. Escovitz, Dr. L. Herman and Dr. A. Wallner, assisted in the study of these cases.

Birmingham Veterans Administration Hospital.

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STUDIES ON SWEAT SECRETION IN MAN

I. Innervation of the Sweat Glands of the Upper Extremity; Newer Methods of Studying Sweating

MARTIN G. NETSKY, M.D.
NEW YORK

PREVIOUS studies of the Smithwick type of preganglionic thoracic sympathectomy have shown an area of anhidrosis on the ipsilateral side of the face, arm and upper portion of the trunk. The loss of sweating has been pictured as complete. The anhidrosis has usually been determined by the method of electrical skin resistance or by colorimetric methods, such as the starch-iodine test. These methods give similar results.[1] In the course of studies with two newer methods, it has been found that the loss of sweating following such an operation is not complete. These methods allow visualization of the function of small numbers of sweat glands and have uniformly shown activity of a small percentage of glands in sympathectomized areas. Evidence is presented that these glands are innervated by preganglionic fibers which arise in the first thoracic root.

METHODS

For purposes of comparison, both the skin resistance method of Richter[2] and the starch-iodine[3] or chinizarin (quinizarin; 1,4-dihydroxy-anthraquinone)[4] method were used. The results reported here are based chiefly on two newer methods. These may be called the tannic acid method and the prism method. The first method has already been described by Silverman and Powell.[5] The

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From the Cushing General Hospital, Framingham, Mass., and the Division of Neuropsychiatry, Montefiore Hospital, New York.

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part to be tested is painted with tincture of ferric chloride and then placed for three minutes on paper impregnated with tannic acid. Where sweating occurs, the iron salt is dissolved out. The resulting formation of ferric tannate leaves an ink spot on the paper. The paper can be applied anywhere on the body. The print is simple to make and gives a permanent record immediately, without the additional step of photography. Details of the method are given in the paper of Silverman and Powell.[5]

The prism method was discovered accidentally. A patient, a former corporal in the Army of the United States, who had had a unilateral thoracic sympathectomy, was handling a triangular prism. He was struck by the difference between the print of his right thumb and that of his left thumb when seen through a face of the prism. In the normal hand, a bright and shiny print, similar to the normal finger print, was observed. On the sympathectomized side, a dull, hazy finger print was seen. Scattered throughout this print, on the ridges where the sweat glands were located, small, bright points were noted (fig. 1). These represented points of moisture produced by sweat glands. This observation was confirmed by direct microscopic study, the possibility that the phenomenon was caused by contact sweating being thus eliminated.

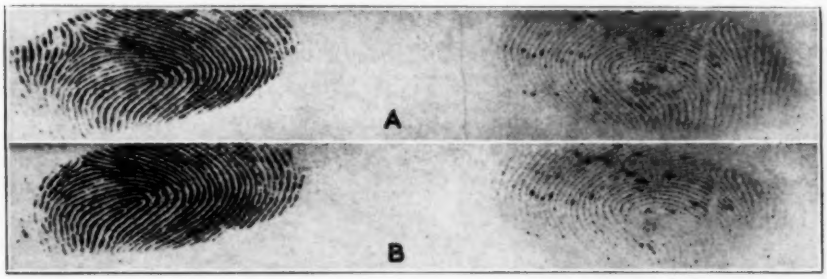

Fig. 1 (S. S.).—Thumbs of the normal (left) and the sympathectomized (right) hand as seen through the prism. Prints *A* and *B* were taken ten minutes apart. Photographs were taken after the thumbs had been on the prism five seconds. The dark spots on the light finger print (right) represent functioning glands. On the left, the relatively large amount of moisture has fused to give the replica of a finger print. Note the slight, but definite, changes on the sympathectomized side over the ten minute period.

A prism with total internal reflection is required in the use of this method. Sweat is easily visualized if the part to be examined is pressed against one face of the prism. Light is then thrown into the second face, and the picture is observed through the third face while the part is held on the prism. The source of illumination for this purpose may be ordinary room light. For permanent recording, photographs are necessary, but may easily be obtained by using an x-ray viewbox with fluorescent or other light (fig. 2). The prism is fixed on the box wth Scotch tape and is surrounded by a black paper mask. The interval between the time the part is placed on the prism and the time of observation should be short, because excess moisture results in smearing and indistinctness. In tests on consecutive areas of the body, the prism should be wiped clean with a soft cloth after each trial.

The simplicity of the method is apparent. A triangular prism is inexpensive and conveniently portable. Both the prism method and the tannic acid method enable one to detect smaller numbers of functioning sweat glands than can be detected by the usual methods. The prism method has the advantage, for some

purposes, of localizing the sweat glands in relation to the ridges of the hand or foot print. Thus, the activity of a few sweat glands can be observed with certainty over a period of time.

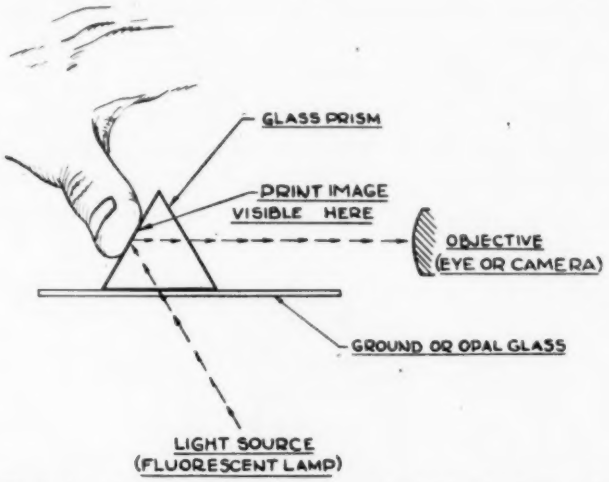

Fig. 2.—Technic of the prism method; method of viewing and recording of sweat prints.

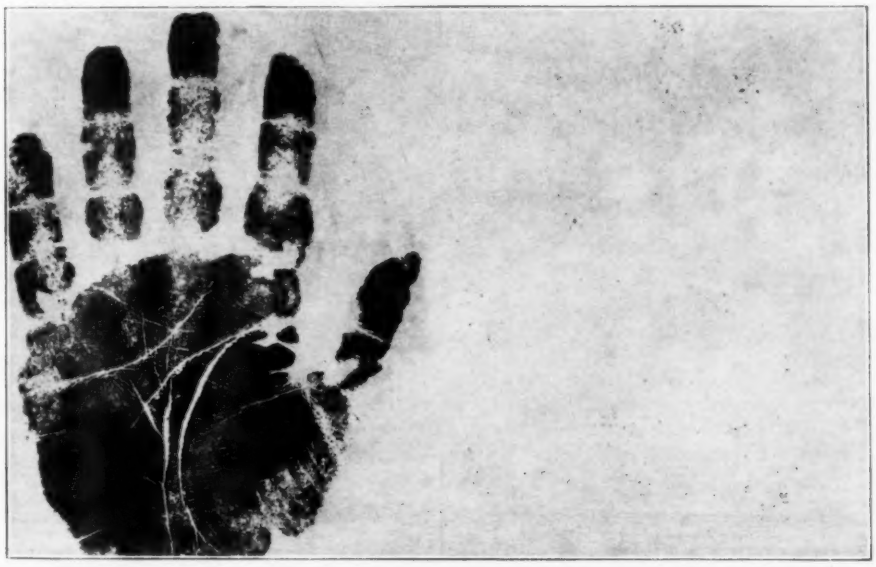

Fig. 3. (S. S.).—Print of the palms with the ferric chloride–tannic acid sweating test one month after thoracic sympathectomy on the right side. Note reduced number of sweat glands functioning in the distribution of both the median and the ulnar nerve on the side of sympathectomy. The left hand shows hyperhidrosis, but a normal sweating pattern.

Studies were made over the entire body, but the majority of examinations were performed on the hands and fingers. Except when it is specifically noted, the patients were not warmed or given drugs to induce sweating, since spontaneous

palmar sweating was usually sufficient. The examinations were made on resting subjects at normal room temperature.

The patients were all male soldiers, ranging in ages from 18 to 35. The principal indication for sympathectomy was causalgic pain.

RESULTS

Fifteen patients with thoracic sympathectomies of the Smithwick type were studied both before and after operation. In all cases, instead of the expected complete anhidrosis, a small number of functioning glands were found scattered throughout the sympathectomized area.

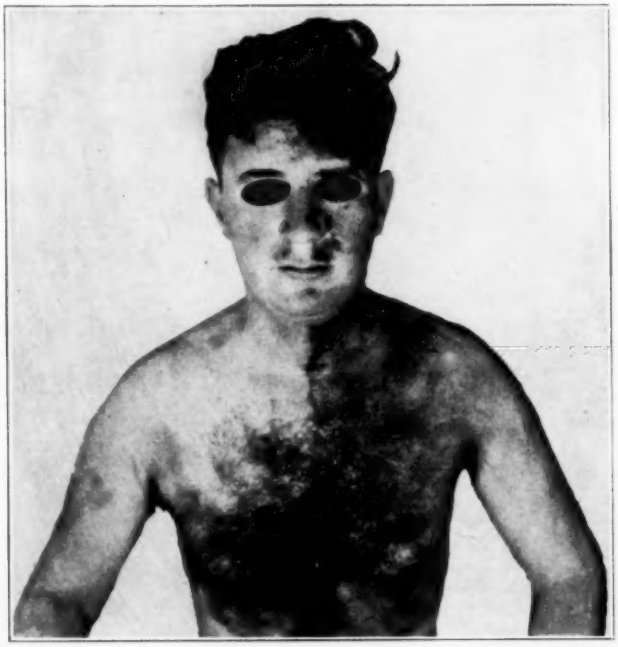

Fig. 4 (A. R.).—Results of the chinizarin (quinizarin) sweating test after thoracic sympathectomy on the right side. Note loss of sweating on the right side of face, the right arm and the right side of the chest above the nipple line. There is hair on the chest above the actual line of demarcation.

Figure 3 shows typical sweat gland function in the palm of a normal and the palm of a sympathectomized hand as determined by the tannic acid method. Figure 1 is the picture seen in the same patient with the prism method, with the thumbs as test objects. In figure 3, on the sympathectomized side, active glands are seen throughout the palm, although they are greatly diminished in number. Active glands were also found on the face and trunk of the same side. The same picture was obtained in patients tested two days after operation, and in other patients up to two years after sympathectomy.

For comparison, the dye methods were used with the patient in the hot room. The usual area of lack of color formation was observed (fig. 4). The skin resistance method confirmed these findings, with the uncolored area showing high resistance and the area with dye coloration low resistance. With sufficient heating, and close observation, a few pinpoint areas of color on the face and trunk were sometimes visible with the colorimetric methods. There was no means of showing these areas by the electrical method. If Kuno's [6] estimate of 500 glands per square centimeter of finger tip is taken, about 2 per cent of the total number of sweat glands was functioning in the sympathectomized finger tip.

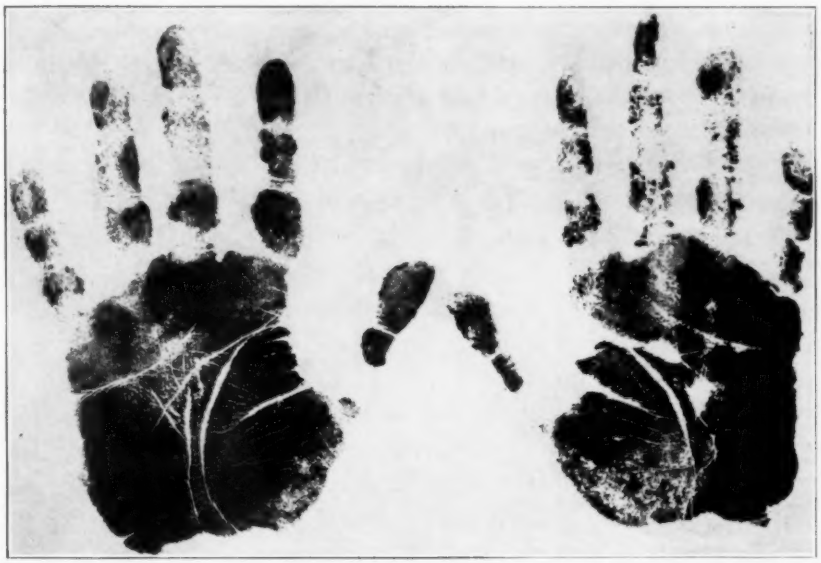

Fig. 5 (S. S.).—Print of palms with the ferric chloride–tannic acid sweating test taken ten minutes after administration of 15 mg., of pilocarpine hydrochloride intramuscularly. Note activation of almost all glands in the sympathectomized hand.

Attention was then directed to study of the mode of activity of the individual glands. Tests were conducted on patients at intervals throughout one day, and from day to day. A typical example of the changes over a single ten minute period is seen in figure 1 *A* and *B*. In both instances the photographs were made five seconds after the thumbs were placed on the prism. Comparison of the two sets of prints shows that while the majority of glands functioning at these times was the same, a few glands had stopped secreting and a few others had begun to function. There was also variation in the volume of secretion from

6. Kuno, Y.: The Physiology of Human Sweating, London, J. & A. Churchill, Ltd., 1934.

some glands. If observed over a sufficient period, any individual gland could be seen to cease functioning temporarily. This picture of alteration in time of function and in volume of secretion is similar to that described by Randall [7] in nonsympathectomized patients.

In 2 cases, the effect of procaine block of the ulnar nerve at the elbow was studied in the sympathectomized hand. This resulted in complete cessation of activity of sweat glands in the distribution of the ulnar nerve. The location of active glands in the palm showed that they were supplied more or less evenly by fibers in the median and ulnar nerves.

In 4 cases intramuscular injection of pilocarpine hydrochloride in doses of 10 to 15 mg. was used to determine the effect on sweating at various intervals after operation. This drug caused activation of the glands throughout the sympathectomized area (fig. 5). Such activation was found in patients from two days to as much as two years after operation. Atropine, as might be expected, caused inhibition of function of the glands.

COMMENT

The presence of active sweat glands in sympathectomized areas may be due to intact fibers or to glands functioning independently of innervation. The inhibition of sweat gland function in the distribution of the ulnar nerve by procaine block at the elbow makes the latter possibility unlikely. Regeneration of fibers must be considered a possible reason for the existence of functioning glands. Against this is the fact that activity was seen in as little as two days after operation. Furthermore, studies on the same patients showed an essentially similar picture during a nine month period. Had regeneration been a factor, a significant alteration of sweating pattern during this time would have been seen.

Using histologic technics, Sheehan [8] found the upper limit of sympathetic outflow from the spinal cord in man to be invariably at the level of the first thoracic root. Van Buskirk [9] described in cats "sinuvertebral nerves" which rise in the vertebral canal to leave by upper thoracic and lower cervical segments. There has been no confirmation of such fibers in man, and against the idea of such a source of sympathetic fibers is the work of Sheehan.

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7. Randall, W. C.: Quantitation and Regional Distribution of Sweat Glands in Man, J. Clin. Investigation **25**:761-767, 1946; Sweat Gland Activity and Changing Patterns of Sweat Secretion on the Skin Surface, Am. J. Physiol. **147**:391-398, 1946.

8. Sheehan, D.: Spinal Autonomic Outflows in Man and Monkey, J. Comp. Neurol. **75**:341-370, 1941.

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In the Smithwick operation,[10] to which these patients were subjected, the sympathetic chain below the third thoracic ganglion is completely severed. Therefore, the fibers innervating the functioning glands cannot come from below the third thoracic root. The white and gray rami communicantes, as well as the anterior and posterior roots of the second and third thoracic levels, are also severed. The cutting of the roots eliminates the possibility of intrathoracic rami rising from below the first thoracic level. This leaves the gray ramus of the first thoracic root as the only likely source of the fibers, it being assumed that no sympathetic fibers leave the cord at levels higher than the first thoracic. Should future work reveal such higher fibers, these would be considered as sources also. But according to present knowledge, the preganglionic fibers of the first thoracic root are the only source of the sympathetic fibers to the upper extremity in these patients.

The contribution of the first thoracic root to the sympathetic innervation of the upper extremity has been discussed by many authors. Kuntz,[11] in a study of cadaver material, came to the conclusion that cutting the first thoracic root was necessary for complete sympathetic denervation of the upper extremity. Using cats and dogs, Kuntz and co-workers [12] reported activation of sweat glands in all parts of the paw pads following electrical stimulation of the anterior root of the first thoracic nerve. However, the question has been raised of the validity of observations on animals in their application to man.

The majority of reports in the literature have stated that in man the first thoracic nerve makes no contribution to the sympathetic innervation of the upper extremity. Ray and co-workers [13] stimulated anterior roots in man and determined the presence of sympathetic innervation by changes in skin resistance of the finger tips. A change was obtained by stimulation of the first thoracic root in only 1 case, and in this case on one side. In 10 other cases, no effect was noted above the second thoracic level. Foerster [14] made a similar study, using vasoconstriction

10. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity: A Preliminary Report, Ann. Surg. **104**:339-350, 1936.

11. Kuntz, A.: Distribution of the Sympathetic Rami to the Brachial Plexus: Its Relation to Sympathectomy Affecting the Upper Extremity, Arch. Surg. **15**: 871-877 (Dec.) 1927.

12. Kuntz, A.; Alexander, W. F., and Furcolo, C. L.: Complete Sympathetic Denervation of the Upper Extremity, Ann. Surg. **107**:25-31, 1938.

13. Ray, B. S.; Hinsey, J. C., and Geohegan, W. A.: Observations on the Distribution of the Sympathetic Nerves to the Pupil and the Upper Extremity by Stimulation of the Anterior Roots in Man, Ann. Surg. **118**:647-655, 1943.

14. Foerster, O.: Operativ-experimentelle Erfahrungen beim Menschen über den Einfluss des Nervensystems auf den Kreislauf, Ztschr. f. d. ges. Neurol. u. Psychiat. **167**:439-461, 1939.

determined by a plethysmograph as a measure of sympathetic innervation. He found that the highest level in the spinal cord which produced vasoconstriction was the fourth thoracic.

Hyndman and Wolkin [15] presented evidence of complete sympathectomy of the upper extremity by removal of the second thoracic ganglion only. Their results were obtained by the starch-iodine method. A similar result was reported in a single case by Atlas,[16] who used observation with the naked eye to determine the presence of sweating. It would be of interest to use these newer methods on patients with this type of operation.

The more or less even distribution of the functioning glands throughout the sympathectomized palm and upper extremity demonstrates the widespread distribution of glands innervated by a single preganglionic source.

Histologic studies by Billingsley and Ranson [17] and Wolf [18] showed that a single preganglionic fiber makes connections with fifteen to thirty sympathetic ganglion cells. These observations are also in agreement with the findings of Kuntz, Alexander and Furcolo,[12] who noted sweating throughout the paw pad in animals after stimulation of single anterior roots. Ray, Hinsey and Geohegan [13] also commented that stimulation of a single root caused changes in skin resistance of all the finger tips of the involved hand.

The activation of sweat glands in cases of recent and old preganglionic sympathectomies should be mentioned as a warning against the use of pilocarpine to determine areas of anhidrosis in all cases. Hyndman and Wolkin [19] expressed the belief that pilocarpine could be used to differentiate between preganglionic and postganglionic sympathectomy. They found that pilocarpine produced sweating in cases of the former but that two months after cutting of postganglionic fibers there was no response of sweat glands to intramuscular injection of the drug. Studies on the postganglionic denervation in cases of peripheral nerve

15. Hyndman, O. R., and Wolkin, J.: Sympathectomy of the Upper Extremity: Evidence That Only the Second Dorsal Ganglion Need Be Removed for Complete Sympathectomy, Arch. Surg. **45**:145-155 (July) 1942.

16. Atlas, L. N.: The Role of the Second Thoracic Spinal Segment in the Preganglionic Sympathetic Innervation of the Human Hand: Surgical Implications, Ann. Surg. **114**:456-461, 1941.

17. Billingsley, P. R., and Ranson, S. W.: On the Number of Nerve Cells in the Ganglion Cervicale Superius and of Nerve Fibers in the Cephalic End of the Truncus Sympatheticus in the Cat and on the Numerical Relations of Preganglionic and Postganglionic Neurones, J. Comp. Neurol. **29**:359-366, 1918.

18. Wolf, G. A., Jr.: The Ratio of Preganglionic Neurons to Post-Ganglionic Neurons in the Visceral Nervous System, J. Comp. Neurol. **75**:235-244, 1941.

19. Hyndman, O. R., and Wolkin, J.: The Pilocarpine Sweating Test: I. A Valid Indicator in Differentiation of Preganglionic and Post-Ganglionic Sympathectomy, Arch. Neurol. & Psychiat. **45**:992-1006 (March) 1941.

injury will be reported in another publication, but it can be stated here that no response to pilocarpine was obtained with complete nerve lesions.

The question arises whether vasomotor fibers remain functioning with the sudomotor fibers. This cannot be answered by data from the present work, since only sweating activity was studied. The possibility should be considered that the failure of the Smithwick type of sympathectomy in some cases may be due to the presence of intact fibers.

SUMMARY

A new method for study of the function of sweat glands is presented. The prism method allows simple and direct visualization of sweat formation, revealing details not found by the skin resistance test or by the usual colorimetric methods. The ferric chloride–tannic acid method of Silverman and Powell is shown to be useful in the study of sweating. With these methods, in 15 cases of the Smithwick type of preganglionic thoracic sympathectomy, the hands showed a small number of functioning sweat glands, estimated in the finger tips at 2 per cent of the total number of glands. These functioning glands exhibited variation in time of function and in output.

Evidence is presented that the intact function of these glands indicates that in man a small supply of preganglionic sudomotor fibers to the upper extremity comes from the first thoracic root. These fibers supply sweat glands throughout the sympathectomized palm by way of the median and ulnar nerves.

The preganglionic sympathectomized areas can be activated by pilocarpine at all times, from two days to at least two years after operation.

Montefiore Hospital, Gun Hill Road.

PERIPHERAL NEUROPATHY IN NEURAL LEPROSY

Report of a Case

JOSEPH PESSIN, M.D.
LOS ANGELES
AND
LIEUTENANT (jg) C. F. KITTLE, U.S.N.R.

ALTHOUGH leprosy is prevalent in tropical climates, the disease in more temperate regions is relatively infrequent. A leprous patient in a temperate climate may not be recognized because of the failure to consider this malady, as well as the difficulties inherent in some cases in establishing a diagnosis.

This report is presented (1) to illustrate the widespread involvement of the nervous system in leprosy, (2) to call attention to the etiologic role of Mycobacterium leprae in peripheral neuropathy and (3) to emphasize the manner in which this type of neural leprosy may resemble other neurologic syndromes.

REPORT OF CASE

F. R., an Italian coal miner aged 57, was admitted to the Veterans Administration Hospital at Los Angeles in October 1946, complaining of weakness in his arms and legs, loss of sensation over the entire body and paralysis of the facial muscles. He dated the onset of his illness to 1921, when he noted slight weakness of his arms as he attempted to hoist objects. The weakness increased progressively to involve his arms, legs and face. Muscular atrophy and loss of sensation accompanied the weakness. Owing to the progressive disability, he was admitted on several occasions to Veterans Administration hospitals, and various conditions were suggested, the diagnosis depending on the predominant signs and symptoms at the time of admission. Definitive diagnosis was not established until smears from the nasal mucusa revealed Myco. leprae.

Clinical Course.—In 1930 the patient injured the lower part of his right leg while loading coal. Although he described this injury as minor, the lower half of the leg became greatly discolored, and shortly thereafter he noted numbness of the right foot and ankle. The numbness ascended gradually, and his skin failed to perspire over the affected area. In 1932 he noted that fine hand movements were difficult, and it was impossible for him to attach dynamite sticks to their fuses or to button his clothing. In 1933 he was unable to dorsiflex his right foot, and at about the same time he noted hyperesthesia of the upper parts of his arms, so that for several weeks he could not endure contact of bedcovers

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or other clothing with his arms. During the same year he had a severe toothache, and the left side of his face became red, but not swollen. His cheek felt numb, and the left side of his face was paralyzed. The numbness spread over the entire face and neck.

The physical and neurologic signs, which were prominent from the onset of his illness until 1935, were progressive weakness and atrophy of the small muscles of the hands, right foot drop and palsy of the left side of the face. The sensory changes were chiefly subjective and received less notice. In view of the aforenoted signs, chronic progressive muscular atrophy was suggested in 1935 as the most probable diagnosis.

In a second mining accident, in 1936, the patient sustained a compound fracture of the lower third of the left tibia and fibula. The fractures healed readily, but subsequently his left foot became numb and the numbness ascended progressively, accompanied with anhidrosis, in the same manner as in the right leg.

On his hospitalization in 1936, examination revealed palsy of the left side of the face, with pronounced atrophy of the facial muscles, weakness of the masseter muscles and patchy hypesthesia over the left side of the face. There was left lagophthalmos with fixation of the left upper lid and ectropion formation. The interosseous muscles of the hands were atrophied. He was unable to clench his fingers, and the grip was weak bilaterally. Fine hand movements were impaired. All deep reflexes were present and equal, though decreased, on the two sides. Sensory examination revealed many patchy and asymmetric areas of anesthesia, more prominent in the distal portions of the extremities. Trophic changes in the legs and face were noted and were presumed to be due to vasomotor disturbances. Ring-shaped, macular areas of erythema, enclosing circles of normal-appearing skin, which were anesthetic, involved the left side of the chest.

The serologic reactions of the blood were negative; the feces were normal, and the sputum revealed no pathogens. The hemoglobin and red and white cell counts were normal. The differential count was 57 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes, 5 per cent monocytes and 14 per cent eosinophils. Examination of the spinal fluid revealed no pleocytosis, a normal reaction for globulin and a Lange gold curve of 1111000000. The Wassermann reaction of the fluid was negative. Examination of the nose at this time showed a normal condition except for a slight deviation of the nasal septum. The diagnosis of syringomyelia was made. Amino-acetic acid, ephedrine and hydrotherapy were prescribed, none of which helped appreciably.

In 1938 the patient entered a state hospital for two months, and in 1939 he was hospitalized at the Marine Hospital, Cleveland. His illness had progressed by this time so that he had extreme weakness of the hands, which were clawlike; inability to dorsiflex either foot; palsy of the left side of the face; areas of hypesthesia widely scattered over the body, and muscular atrophy of the hands, arms, lower parts of the legs and face. A presumptive diagnosis of leprosy was made. Many microscopic preparations of skin from the trunk and abdomen were examined at this time, but no Myco. leprae organisms were found. The patient was told that he did not have leprosy and was discharged.

He was hospitalized in 1945 because of slight hemoptysis and pleurisy. Repeated examinations of the sputum did not reveal tubercle bacilli, and no clinical evidence of tuberculosis was found.

Two weeks prior to his last admission, in October 1946, the patient sustained third degree burns over the sacral region while warming himself before an open

fire and recalled that for about the past ten years he had been unable to differentiate heat from cold and had suffered severe burns on many previous occasions.

A persistent feature had been the invariable exacerbation and exaggeration of his symptoms during cold, rainy or damp weather and the constant amelioration during warm or dry periods. Before coming to California, the patient was unable to exert any control over the orbicularis oris, food and water dribbling on his chin. He was also unable to extend his arms over his head or directly before him and frequently had difficulty in walking. Since being in California, he had felt stronger and had recovered a small amount of his motor ability.

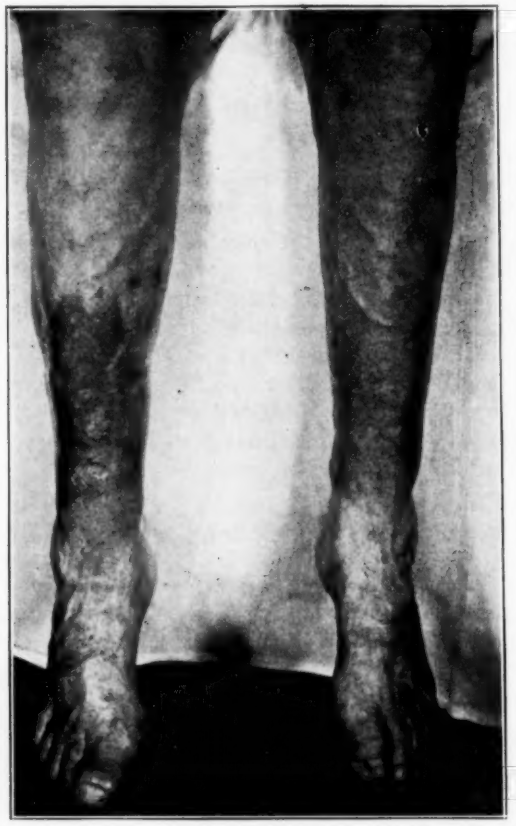

Fig. 1.—Photograph of the lower extremities, illustrating the trophic disturbances (glossiness, pigmentation and changes in the toe nails), superficial varices, edema and bilateral foot drop. The muscular atrophy is not obvious because of the edema.

Past and Family Histories.—The patient had influenza in 1919, "boils" on his face and neck in 1920, a ruptured appendix and appendectomy in 1929 and a hemorrhoidectomy in 1936. At the age of 5 months he sustained a severe burn on the lower part of his back. He recalled no unexplained febrile illnesses or attacks of epistaxis.

Although born in Italy, the patient emigrated to South America at the age of 14 and lived in Brazil for several years. His family next moved to the United States, where the patient lived in Ohio, Pennsylvania and Kentucky. He served overseas during the first world war, being in combat in France and Germany.

His father died in 1911, after an accident, and details of his death are obscure. His mother died in 1942, of "old age." Three brothers were living and well, 2 living in Italy and 1 in the United States. The patient was married in 1922. His wife, aged 45, was living and well. The couple had 5 children, all of whom were reported to be in good health.

General Examination.—The patient presented a bizarre appearance. His arms dangled limply at his sides. He stood with his feet wide apart and walked with a steppage gait. The blood pressure was 136 systolic and 70 diastolic. The heart, lungs and abdomen showed no abnormalities.

The skin of the extremities presented many atrophic variations, characterized by large and small areas of thickening, atrophy, glossiness, "cross hatching" and

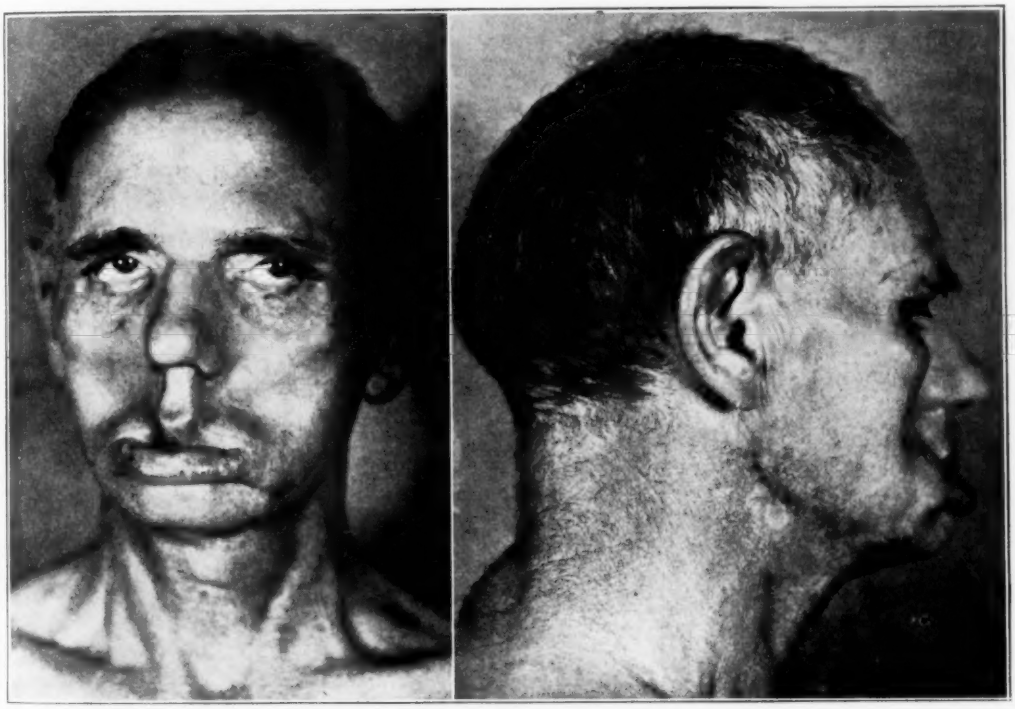

Fig. 2.—Front and profile views of the face and neck, portraying the weird expression caused by the facial diplegia, bilateral atrophy and lagophthalmos. Note the outward flaring of the lower lip and the pronounced involvement of the orbicularis oris. (The scar present in the right cervical region is a remnant of the "boils" experienced in 1920. The apparent superciliary alopecia seen in the profile is residual from an accident.)

"onion skin" changes. These were more extensive in the legs than in the arms (fig. 1). The skin of the lower halves of the legs exhibited brown pigmentations. Both the finger and the toe nails showed trophic disturbances. There were large scars of the lower lumbar and sacral areas secondary to third degree burns. No nodular or macular lesions suggesting active or residual cutaneous leprosy were seen. No alopecia could be found.

Neurologic Examination.—The olfactory sense was intact bilaterally. The pupils were round and equal and responded promptly to light and in convergence.

The visual fields were intact, and normal ocular movements were present. Visual acuity was 20/100 in each eye. There was bilateral loss of sensation to cotton and pinpoint over the area supplied by the trigeminal nerve. The muscles of mastication presented diminished strength. The facial diplegia, bilateral lagophthalmos and ectropion formation caused a grotesque facial expression, which was accentuated by the marked protrusion of the lower lip (fig. 2). Excessive lacrimation was present. There were no demonstrable changes in the vestibular and auditory nerves. The gag reflex was intact, and the uvula ascended in the midline. Speech was muffled and difficult to understand, owing to paralysis of the orbicularis oris and atrophy of the cheek and facial muscles. The tongue showed no atrophy, fibrillation or paralysis. Muscular atrophy of the upper extremities was more prominent distally than proximally. The hands were contracted in typical main de griffe (fig. 3). The patient was able to lift his arms above his head only with difficulty.

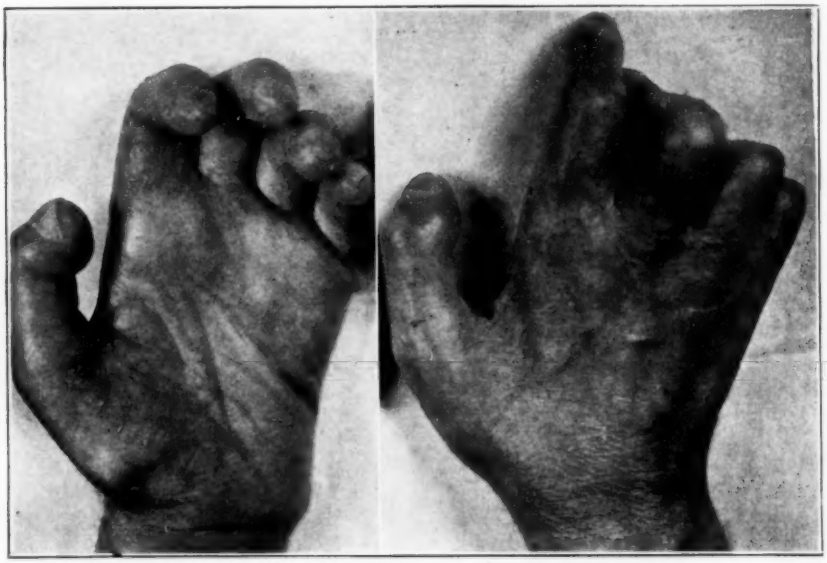

Fig. 3.—Hands, showing atrophy of the thenar, hypothenar and interosseous muscles and the trophic changes in the skin and nails. The main en griffe is typical of leprosy.

In addition to the cutaneous changes already mentioned, the lower extremities showed many superficial varices, slight pitting edema, bilateral foot drop and muscular atrophy.

The biceps and triceps reflexes were inconstantly elicited, being absent on his admission and present after a period of hospitalization. The achilles reflex was absent, and the patellar reflex was elicited only with reenforcement. The superficial reflexes were intact. It was difficult to obtain an accurate sensory response, but after repeated testing it was believed that complete loss of pain and temperature sense was present over the entire body except for the scalp. Light touch sense was generally diminished, with a few scattered normal reactions over the trunk. It was absent on the face. Vibratory sense was diminished in the lower extremities. Some examiners stated the belief that the right ulnar nerve could be palpated; others could not feel it. There were no other palpable nerves. Muscular fibril-

lation was not evident. No abnormality of the patient's mental status was present other than a mild depression, which was attributed to the patient's knowledge of his disease and its social implications.

Laboratory Studies.—The blood count showed 5,400,000 red cells, 9,400 white cells and 100 per cent hemoglobin. The Wassermann reaction of the blood was negative. A roentgenogram of the chest was interpreted as showing minimal tuberculous scarring in the apex of the right lung without evidence of activity; mild pulmonary emphysema was evident at the bases of both lungs. Roentgenologic studies of the carpal bones showed cystic changes, with roughening of the articular cortices and generalized demineralization. This condition was interpreted as secondary to a neuropathy. Moderate hypertrophic arthritis was noted involving the fifth,

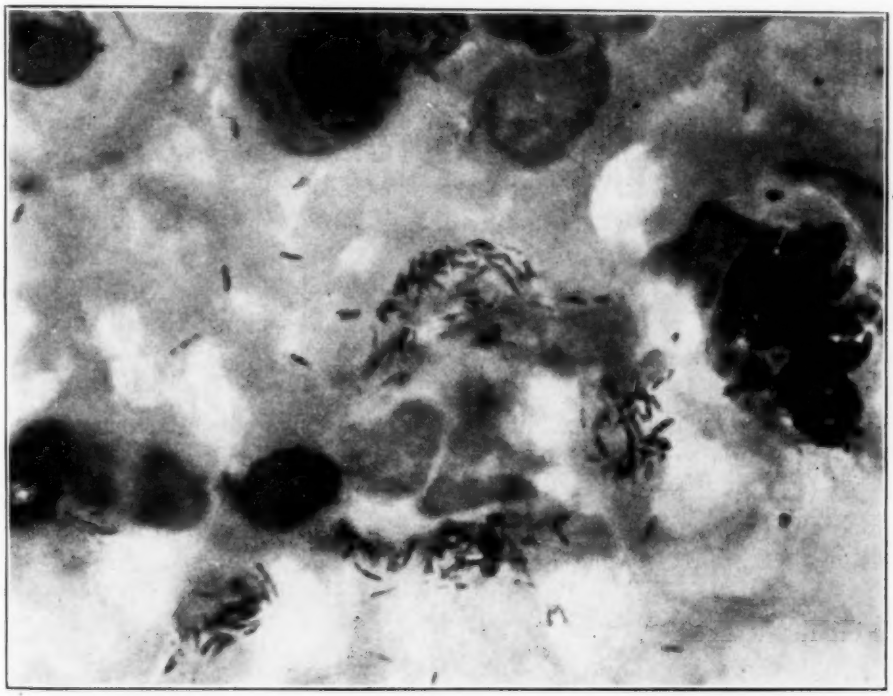

Fig. 4.—Photomicrograph of a nasal smear. Numerous Mycobacterium leprae organisms are seen. Observe their tendency to clump together like a "bundle of cigars." Ziehl-Neelsen stain.

sixth and seventh cervical vertebrae. Nasal examination revealed a small area of crusting on the anterior part of the right naris. This was removed and a superficial ulcerated area was found. A smear from this lesion showed numerous Hansen's bacilli on several occasions (fig. 4).

During the patient's hospitalization no specific type of treatment was given, and he was removed to the National Leprosarium, at Carville, La., on March 5, 1947.

COMMENT

The progression of neurologic signs and symptoms suggested several diagnoses to various examiners who saw this patient at different stages in the disease process. The presence of atrophy of the hands, forearms,

upper arms, face and, to a lesser degree, the lower extremities, associated with weakness and diminished deep reflexes, suggested chronic progressive muscular atrophy (Aran-Duchenne type) to some examiners. The history of subjective sensory disorder and the subsequent appearance of objective sensory disability are not compatible with the diagnosis of chronic progressive muscular atrophy.

The sensory disturbances were more prominent when the patient was hospitalized in 1936. On this admission, attention was focused on the history of painless burns, the presence of trophic changes in the skin and nails and muscular wasting, especially in the distal portions of the upper extremities. At this time a diagnosis of syringomyelia was made, and this diagnosis seemed most plausible until Hansen's bacilli were isolated from the nasal secretions.[1]

The differential diagnosis of syringomyelia and leprosy is a difficult one. Grinker[2] commented briefly as follows: "Leprosy of the anesthetic type is differentiated by characteristic skin lesions and thickened peripheral nerves in which Hansen's bacilli are found." In our patient there were no "characteristic skin lesions" at this late stage of the disease process.

It has been mentioned previously that microscopic specimens of skin were examined for the Myco. leprae in 1939, with negative results. In this connection, it is important to emphasize that the well trained leprologist may experience difficulty in diagnosing a cutaneous lesion as that of leprosy when the organisms are scarce or absent.[3] Hence, a negative report in the presence of cutaneous and neurologic changes should not eliminate the diagnosis of leprosy. The failure to isolate the Myco. leprae in 1939 and the successful demonstration of these organisms in 1946 also suggest the need for repeated and careful laboratory procedures.

Wilson[4] offered the following differential criteria:

> Among the nervous diseases, syringomyelia, perhaps, stands most in need of differentiation, but the two are quite distinct, lepra being peripheral and the other spinal. The sensory loss of the latter, and its often completely dissociated type, are not paralleled by leprous forms, where the changes follow peripheral lines and are more limited or patchy; deep sensibility is unimpaired in leprosy (as a rule) nor do nystagmus and paraplegia occur, while its peculiar facial palsies and thickened nerves also aid diagnosis. Atrophic feet may characterize leprosy, but seldom, if

1. Credit for suggesting the diagnosis of leprosy is due Dr. Alan C. Ellerding, resident in medicine, Veterans Administration Hospital, Los Angeles.

2. Grinker, R. R.: Neurology, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1944.

3. Fite, G. L.: Personal communication to the authors.

4. Wilson, S. A. K., and Bruce, A. N.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 1.

ever, syringomyelia, and muscular wasting never begins at the shoulder girdle in the former. The leper's gait is not spastic, but "neuritic" with a tendency to drop foot.

The differentiating features related by Wilson which seemed most applicable to the present case are the peculiar facial palsy, seen in figure 1; the "neuritic" gait, and the presence of foot drop.

Strong [5] summarized as follows:

In syringomyelia, however, the upper extremities are, as a rule, alone affected, and the muscular atrophy is more of the scapulohumeral type with involvement of the trunk muscles causing scoliosis, rather than of the thenar and hypothenar eminences, so that while the fingers may be more contracted and rigid than in leprosy, the main-en-griffe is not produced. The anaesthetic areas of syringomyelia continue to sweat, and there may be also spastic symptoms and speech defects in syringomyelia, but, even so, the differential diagnosis may be sometimes especially difficult.

It is significant to point out that our patient exhibited the main en griffe disability (fig. 3) and that he lost the ability to sweat, two signs unlikely to occur in syringomyelia.

Piatnizky and Schakhonovitch [6] reported an interesting clinical case that presented a problem in differential diagnosis of syringomyelia and leprosy. At autopsy, lepra bacilli were observed in the viscera, and a distinct cavity existed in the cervical enlargement of the spinal cord. The radial, ulnar, median, sciatic, tibial and peroneal nerves "revealed nodular tumefaction and fragmentation of the myelin with marked fibrosis of the endoneurium, perineurium and epineurium. . . . The membranes of the nerves (especially the tibial) were hyperplastic and infiltrated with lymphocytes." The authors concluded that there were two independent pathologic processes: leprosy which caused an "interstitial neuritis" and cavitation in the cervical cord; "the cavity was evidently a manifestation of a congenital anomaly, such as syringomyelia, and was an accidental complication."

Earlier publications, specifically those of Zambacho-Pacha,[7] Pestana and Bettencourt [8] and Langhans,[9] expressed the belief that syringo-

5. Strong, R. P.: Stitt's Diagnosis: Prevention and Treatment of Tropical Diseases, ed. 7, Philadelphia, The Blakiston Company, 1944, vol. 1.

6. Piatnizky, N. H., and Schakhonovitch, R. A.: A Clinical and Neuropathological Report of a Case of Lepra Mixta, Arch. Neurol. & Psychiat. **20**:602 (Sept.) 1928.

7. Zambaco-Pacha: Etat de nos connaissance actuelles sur la lepre, Semaine méd. **13**:289, 1893.

8. Pestana, C., and Bettencourt: Ueber die Anwesenheit des Leprabacillus in der Medulla eines an Syringomyelitis gestorbenen Individuums, Centralbl. f. Bak. **19**:698, 1896.

9. Langhans: Sur Causistik der Ruckenmarks-Affectionen, Virchows Arch. f. path. Anat. **64**:169, 1875.

myelia and leprosy were etiologically related, but this view is not accepted currently.

As a suggestion in arriving at a definite differentiation of leprosy and syringomyelia, Strong [5] stated that ". . . the bacteriological examination and finding of leprosy bacilli is the most satisfactory means of the differentiation of these two diseases."

In the absence of postmortem confirmation, it is not possible to determine whether the patient whose case is described has one or two disease entities, but we believe that his neurologic status may best be explained on the basis of pathologic changes associated with leprosy.

SUMMARY AND CONCLUSIONS

1. A case of neural leprosy, undiagnosed over a period of twenty years, is presented.

2. The problem of differentiating neural leprosy from other neurologic disorders, especially syringomyelia, is illustrated and discussed.

3. The difficulty of establishing a definite diagnosis in neural leprosy is presented.

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UNRELATED NEUROLOGIC SYNDROMES IN PATIENTS WITH SYPHILIS

E. R. MAILLARD, M.D.
NEW YORK

ERRONEOUS diagnoses of neurosyphilis are sometimes made in cases of neurologic syndromes because of a history and serologic evidence of syphilis and the presence of abnormalities in the cerebrospinal fluid. It is generally recognized that examination of the cerebrospinal fluid is essential for the diagnosis of neurosyphilis. As shown in a previous report,[1] the reagents and procedures used in such tests should be quantitatively standardized in order to yield accurate and reproducible results. They should include a cell count, determination of total protein and a colloidal gold test of the cerebrospinal fluid, as well as quantitative complement fixation tests of both the cerebrospinal fluid and the blood.[2] Furthermore, the results of the tests of the cerebrospinal fluid should have a quantitative relation to each other, so that together they form a syndrome reflecting the activity and character of the syphilitic inflammatory process. The result of each test should be evaluated as a part of the whole. This is particularly true of the result of the complement fixation test.

There is evidence to indicate that the reagin in neurosyphilis is formed within the central nervous system and that permeation of the blood colloids into the cerebrospinal fluid does not occur normally.[3] In pathologic conditions involving the vessels of the central nervous system, however, the barrier between the blood and the cerebrospinal fluid may be altered and allow an admixture of blood protein with cerebrospinal fluid. Knowledge of this alteration in permeability and of

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From the Division of Laboratories and Research, New York State Department of Health, Branch Laboratory, 339 East Twenty-Fifth Street.

1. Maillard, E. R., and Orzel, A.: The Value of Quantitatively Standardized Tests in Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:506 (Sept.) 1947.

2. Wadsworth, A. B.: Standard Methods of the Division of Laboratories and Research of the New York State Department of Health, ed. 3, Baltimore, Williams & Wilkins Company, 1947, pp. 361-465, and 517-538.

3. Katzenelbogen, S.; Rogovine, S., and Monedjikova, V.: The Relation Between the Wassermann Reactions in the Blood and in the Cerebrospinal Fluid: A Contribution to the Question of the Origin of the Antibodies, Arch. Neurol. & Psychiat. **21**:376 (Feb.) 1929.

admixture of plasma with cerebrospinal fluid is essential to a proper evaluation of the laboratory results. Evidence of increased permeability will be indicated partly by the character of the colloidal gold curve, in that the maximum reaction is obtained in the sixth or in a higher dilution of the cerebrospinal fluid. This shift to the right of the point of maximum reaction is characteristic of the curve designated as C, formerly classified as the meningitic, or third zone, curve. In addition, there will be a relatively high protein value, while the cells may or may not be increased. If the neurologic process is unrelated to syphilis, no reaction in the complement fixation test with the cerebrospinal fluid should be expected except when the reagin titer of the blood is relatively high and plasma has gained access to the cerebrospinal fluid in sufficient amount to give a reaction.

In cases of primary and secondary syphilis, an increase in the number of cells is usually the first abnormality noted in the cerebrospinal fluid, and this frequently occurs before a reaction is obtained with the complement fixation test. In such cases, however, the total protein values and colloidal gold reactions may be within normal limits, or slightly increased. With later, or more advanced, active neurosyphilis, higher values may be expected in all the tests, but in general they, too, will have a quantitative relation to each other.

When the cause of the neurologic abnormalities is in doubt, and a patient has a history or serologic evidence of syphilis, there is always the temptation to make a diagnosis of neurosyphilis when the cerebrospinal fluid findings are distinctly abnormal. One should be skeptical, however, when there is no reaction in the complement fixation test for syphilis with the cerebrospinal fluid, or when the degree of reaction is low and the findings indicate the probability of an admixture of blood proteins in the presence of a relatively high reagin titer of the blood.

REPORT OF CASES

CASE 1.—*Increased vascular permeability believed to have resulted from a neurovirus infection.*

A man aged 22 stated that he had had double vision for about two months and a constant pain in the back of the neck, head and eyes. He had experienced progressive generalized weakness with loss of appetite and weight—about 10 to 15 pounds (5 to 7.5 Kg.) in the last month. He gave a history of chancre at the age of 16. He had been receiving weekly injections of a bismuth and arsenic preparation for the past eight months. Examination showed diplopia, tenderness of the eyeballs, drowsiness, stiffness of the neck, weakness of the left external rectus muscle, sluggish reaction of the right pupil to light and slight weakness of the right side of the face. The right upper and left lower extremities were paretic, and the deep reflexes were diminished. The abdominal skin reflexes were absent. Sensation was intact. The first clinical impression was that of neuro-

syphilis, but the diagnosis was subsequently changed to lymphocytic choriomeningitis. Specimens of the cerebrospinal fluid and the blood were examined in March, April and May 1946. The results are given in table 1.

CASE 2.—*Increased vascular permeability, attributed to the action of a chemical agent.*

A young woman aged 21 was treated for secondary syphilis with penicillin and oxophenarsine hydrochloride U. S. P. On the eighth day of treatment, the patient complained of dizziness, became stuporous and was unaware of her surroundings.

TABLE 1 (case 1).—*Serologic Data in a Case of Latent Syphilis (Lymphocytic Choriomeningitis)*

	Blood,	Cerebrospinal Fluid												
					Colloidal Gold Test‡									
Date Collected	Complement Fixation Test*	Complement Fixation Test*	Cells†	Total Protein, Mg./100 Cc.	15	23	34	51	76	114	171	256	384	576	Total
3/ 5/46	..	None	725	197	2	3	4	5	7	10	15	16	15	9	86
4/26/46	13	None	88	124	6	8	9	13	15	16	17	16	15	10	125
5/ 9/46	12	None	19	121	6	8	9	10	15	16	17	16	15	8	120

* Quantitative complement fixation test with cardiolipin antigen, read in titers.
† Mononuclear cells per cubic millimeter.
‡ The reaction obtained with each dilution of cerebrospinal fluid is compared with a color standard given numerical values ranging from 0 to 20.

TABLE 2 (Case 2).—*Serologic Data in a Case of Secondary Syphilis and Toxic Meningoencephalopathy (Arsenical)*

	Blood,	Cerebrospinal Fluid												
					Colloidal Gold Curve‡									
Date Collected	Complement Fixation Test*	Complement Fixation Test*	Cells†	Total Protein, Mg./100 Cc.	15	23	34	51	76	114	171	256	384	576	Total
7/12/46	59	4	47	243	4	5	5	6	7	9	13	15	9	8	80
7/18/46	57	None	38	69	4	5	7	8	9	9	8	6	5	3	65
9/10/46	3	....	...	...											

* Quantitative complement fixation test with cardiolipin antigen, read in titers.
† Mononuclear cells per cubic millimeter.
‡ The reaction obtained with each dilution of cerebrospinal fluid is compared with a color standard given numerical values ranging from 0 to 20.

Her temperature rose to 104 F., and the pulse rate increased to 118 a minute. Pronounced nuchal rigidity and a generalized purpuric eruption were noted. Convulsive seizures followed, each lasting about two minutes. The patient was stuporous but not in a coma. The pupils were small and equal and reacted promptly to light. The right fundus showed slight increased vascularization of the disk. No hemorrhages or exudates were seen. No abnormalities were noted in the left fundus. The biceps jerk was present bilaterally, but was depressed. The knee jerk was absent. Periocular edema was noted. The diagnosis was toxic meningoencephalopathy, due to arsenic. Two specimens of blood and cerebrospinal fluid each were examined eight and fourteen days after the initial symptoms of neurologic involvement. A third specimen of blood was examined one month later. The results are given in table 2.

COMMENT

Both these patients gave a history and serologic evidence of syphilis. In addition, they manifested clinical evidence of a neurologic disturbance, the cause of which was to be determined. Tests of the cerebrospinal fluid indicated an inflammatory process of the central nervous system, but the syndrome as a whole did not suggest syphilis as the most probable cause of the process. The pronounced increase in cells, the high protein values and a type C ("meningitic") curve for the cerebrospinal fluid reflected an inflammatory process of such intensity that if due to syphilis it would be expected to yield a correspondingly strong reaction in the complement fixation test for syphilis. The cerebrospinal fluid syndromes in both these cases were sufficiently atypical for neurosyphilis to suggest that some condition other than syphilis was responsible for the abnormal findings.

CONCLUSION

It has been shown that abnormal changes in the cerebrospinal fluid of patients with syphilis who have clinical evidence of lesions in the central nervous system may be incorrectly interpreted as evidence of neurosyphilis. To avoid such erroneous conclusions, it is essential that the laboratory examinations include a cell count, determination of total protein, colloidal gold test of the cerebrospinal fluid and complement fixation tests of both the cerebrospinal fluid and the blood. These tests should be quantitatively standardized to yield accurate and reproducible results. Furthermore, the results of laboratory examinations should be correlated and classified in accordance with the type of syndrome which they represent.

339 East Twenty-Fifth Street.

Case Reports

PAROXYSMAL CEREBRAL DYSRHYTHMIA FOLLOWING LARGE DOSES OF POTASSIUM CHLORIDE

MADELAINE R. BROWN, M.D.
Instructor in Neurology, Harvard Medical School
BOSTON

REPORT OF CASE

History.—A man aged 47 was seen first on Sept. 14, 1942. For two months he had staggered when walking, and any movement of the head caused dizziness.

The present illness began in August 1939, when he had his first attack of severe vertigo with vomiting. This came on suddenly when he was standing on the street outside a store. He had several severe attacks after this one and was treated by his local physician for six months. He was seen at a clinic in February 1940, where a low sodium diet and ammonium chloride were prescribed. He had shown much improvement until the summer of 1942, when he consulted his family physician because of staggering and dizziness. He had stopped taking the ammonium chloride for some time before but still maintained the low sodium intake. His blood count was normal, and repeated urinalyses showed nothing abnormal. The Wassermann, Hinton and Kahn tests gave negative reactions. The blood pressure was 140 systolic and 98 to 90 diastolic. The heart and lungs were normal. He was sent to an otolaryngologist, who made the diagnosis of nerve deafness. On July 1, 1942, he was placed under treatment with 6 Gm. of potassium chloride a day. Phenobarbital, up to 3 grains (0.195 Gm.) a day, was prescribed, and he was instructed to continue the restriction of salt intake. His symptoms had improved since he had started the potassium chloride therapy.

The past history revealed that he had had no severe illness. He was married and had no children.

There was no family history of epilepsy, migraine or deafness in the family. One sister was in a psychiatric hospital with a psychosis which had started during the puerperium. His other brothers and sisters were living and well.

Neurologic Examination.—The patient was tense and agitated concerning his symptoms and mentioned the possibility of operation. The fundi and pupils were normal. The extraocular muscles were normal; there was no nystagmus or diplopia. Hearing was slightly reduced on the left. Both air and bone conduction were affected. The Weber test revealed nothing abnormal. He said that he had an occasional crackling sound in the left ear. There was no loss of strength, coordination or sensation in the arms or legs. The deep reflexes were active and equal on the two sides; the plantar response was normal.

Diagnosis.—The diagnosis was Ménière's syndrome, in partial remission.

Treatment and Course.—It was recommended that the dose of potassium chloride be increased to 2 Gm. six times a day for three weeks and that he discontinue the low sodium diet but add no salt to his food at the table and eat no heavily salted foods.

On Oct. 5, 1942, he stated that he felt a great deal steadier on his feet and that he had had no digestive disturbances from taking the 12 Gm. of potassium chloride per day. On November 13 he stated that he was feeling still better but

had had one or two brief attacks of "falling forward" unassociated with dizziness. He had caught himself before he reached the floor.

On March 18, 1943, his dizziness had practically disappeared, but he had had one incident of falling forward while walking on the street, and this time he could not bring himself upright for a minute. He believed he had been momentarily unconscious. His dose of potassium chloride was reduced to 9 Gm. a day, and an electroencephalographic recording was ordered. The report from the Massachusetts General Hospital stated that the record showed irregular, 9.5 per second alpha rhythm and some beta activity. Voltages in the right parietal and occipital regions were higher than those on the left. Overbreathing for three minutes produced no significant changes in the record until the third minute. At that time some relatively prominent slow waves appeared in the occipitoparietal region. The whole appearance of the record was ragged and spiky.

On May 13, 1943, he had had no attacks of any kind, and the dose of potassium chloride was reduced to 1 Gm. six times a day. He was maintained on this dosage without any attacks until Jan. 25, 1944. At this time he had a fainting spell on the sidewalk. He fell on his back but was able to pick himself up and walk off. He was given 0.1 Gm. of phenobarbital per day and was maintained on the 6 Gm. of potassium chloride.

In August 1944 the dose of potassium chloride was reduced to 3 Gm. a day, since he had had no attacks of vertigo. In November 1944 he had had two attacks of falling but stated the belief that he did not completely lose consciousness. At this time treatment with 2 capsules (0.1 Gm. each) of diphenylhydantoin sodium per day was begun. Up to September 1945 he had had no attacks of any kind; the potassium chloride was discontinued but administration of 2 capsules of diphenylhydantoin was maintained.

On June 12, 1947, a second electroencephalogram was made, for it seemed possible that the large doses of potassium chloride had been related to his cerebral dysrhythmia. The dose of potassium chloride had been reduced to 3 Gm. thirty-four months before; he had received none for twenty-one months and had had no loss of consciousness for thirty-one months. The report from the Massachusetts General Hospital stated that the record was normal. Overbreathing for three minutes produced no change in the electroencephalogram. Comparison of this record with the earlier one, of March 19, 1943, showed that the two were much alike except that the later one contained far fewer artefacts, did not break down on overbreathing and showed normal activity in the right parietal region and only questionable disturbances in the right occipital region. After this report, the diphenylhydantoin was discontinued.

On April 4, 1948, the patient stated that he had had no lapses of consciousness and that he had noticed little, if any, dizziness during recent months.

SUMMARY

A man aged 47 had been given large doses of potassium chloride for Ménière's syndrome from July 1942 until August 1944. On Nov. 13, 1942, he had two brief attacks of "falling forward." The electroencephalogram taken after hyperventilation showed slow waves in the occipitoparietal region. He continued to have these brief lapses of consciousness until the dose of potassium chloride was reduced, in August 1944. The electroencephalogram taken twenty-one months after potassium chloride had been stopped showed a normal record, with no breakdown on hyperventilation. It is probable, therefore, that the cerebral dysrhythmia was related to the large doses of potassium chloride.

264 Beacon Street (16).

Obituaries

ABRAHAM MYERSON, M.D.

1881-1948

With the death of Dr. Abraham Myerson, on September 3, neuropsychiatry has lost one of its most brilliant and colorful figures. Dr. Myerson was endowed with a superior intellect, an insatiable curiosity, a keen power of observation and boundless energy. These gifts, combined with an unusual articulateness, enabled him to express himself on a wide variety of psychiatric subjects. He had a breadth of view which transcended any one school of thought. He was forthright and fearless in his criticism of what he believed to be the too rigid and too exclusive acceptance of the present day concepts of psychodynamics. The following quotation from one of his recent writings (*Quart. Rev. Psychiat. & Neurol.* **3:** 379-382 [July] 1948) expressed his essential approach to man:

"To me Man is a thickened node in the visible and invisible web of a universe of forces which, ever repetitively and ever new, flows in and out of him. He is part of an Ecology which involves plants, other animals, climate, soil, all kinds of radiant forces and chemicals. He is united by the invisible network of Heredity to every form of life that ever lived, and his fundamental drives and compulsive activities go back to the first piece of life that ever appeared on earth. He is immersed in age-old and ever-changing social forces which compress, enhance, destroy or deform his trends. He is beset by conflict between his biology and his sociology at every step. He is the victim and the profiteer of his cunning hands and his fatal words, especially words, the most important of which are I, You, They, and the most fatal, You, when the man learns to address himself by this ominous term. He is abrim with chemical factories; in fact, every cell is a better chemist and physicist than all the Nobel prize laureates put together. Somehow there is a constant and shifting balance of forces within him which include hormones, ferments, enzymes, memories, ideas, emotions, moods, and all of which is an unexplainable transit from conception to that catalytic dispersal, perhaps reassemblage, called Death."

Whether as neurologist, psychiatrist, sociologist, psychologist or teacher, Dr. Myerson left on all who came in contact with him the impact of a warm, human, understanding personality. His inquisitive mind carried him into many fields of study and research. His countless scientific papers attest to his polymorphous activities. His scientific interests ranged from the introduction of the technic of internal jugular

venous puncture, one of the classic approaches to the study of the metabolism of the brain, to his studies on inheritance of mental disease, one of the pioneer American works on this subject.

Born in Yanova, Lithuania, Nov. 23, 1881, Abraham Myerson came to the United States at the age of 5 years. He married Dorothy Loman on March 9, 1913 and had three children: two sons, both psychiatrists, Dr. Paul G. and Dr. David J., and a daughter, Anne.

After graduation from Tufts College Medical School in 1908, he at once became deeply devoted to neurology and psychiatry. He served as resident neurologist at the Alexian Brothers' Hospital in St. Louis in 1911-1912; resident at the Boston Psychopathic Hospital in 1912-1913; clinical director and pathologist at the Taunton State Hospital from 1913 to 1917; director of the outpatient department, Boston Psychopathic Hospital from 1917 to 1919; visiting neurologist, Boston City Hospital from 1919 to 1938; assistant professor of neurology, Tufts College Medical School from 1918 to 1921, and professor of neurology, Tufts College Medical School from 1921 to 1940, when, on his resignation, he was appointed professor emeritus. From 1934 to 1945 he was clinical professor of psychiatry at Harvard Medical School. In 1935 the Commonwealth of Massachusetts set up a special research laboratory building and staff for him at the Boston State Hospital, appointing him director of research, thus rewarding his zealous efforts under inadequate laboratory conditions since 1927.

Dr. Myerson was an exceedingly active member in many national scientific and medical societies. He was chairman of the Committee of the American Neurological Association for the Investigation of Eugenical Sterilization (1934-1935). He was chairman of the committee on research of the American Psychiatric Association from 1939 to 1947. In 1941-1942 he served as vice president of the American Neurological Association. He was representative of the American Psychiatric Association to the National Research Council from 1942 to 1946. He was a certified specialist of the American Board of Psychiatry and Neurology, a member of the American Association for the Advancement of Science, the American Medical Association, the American Psychological Association, the American Psychopathological Association and other state and local groups.

During World War II he gave unstintingly of his time as an examiner for the induction board and served as a consultant to the National Research Council. He was a member of the Advisory Council on Research in Nervous and Mental Disease of the United States Public Health Service, the Commission of the Association for Research in Nervous and Mental Disease and the Scientific Committee of the Research Council on Problems of Alcohol.

Dr. Myerson was also well known for his testimony in some of the widely known legal cases in this country, such as the Sacco-Vanzetti case and, more recently, the Douglas Chandler treason case.

His many scientific writings included work on the inheritance of mental disease, feeblemindedness, the pharmacology of the autonomic nervous system, the biochemistry of the brain, alcoholism, the sexual constitution of man as studied by the hormones, and the treatment of mental disease, including the "total push" method, electric shock therapy and lobotomy. He was the author of "The Nervous Housewife"; "The Foundations of Personality"; "The Inheritance of Mental Diseases"; "When Life Loses Its Zest"; "The Psychology of Mental Disorders"; "The German Jew—His Share in Modern Culture" (with I. Goldberg); "Social Psychology," and "Eugenical Sterilization."

Science and medicine have lost a devoted disciple, and mankind is deprived of a good friend.

News and Comment

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following specialists were certified by examination in San Francisco in October 1948:

Psychiatry.—Joseph Biernoff, San Francisco; L. Bryce Boyer, Berkeley, Calif.; William A. Boyle, Georgetown, Colo.; Woodrow W. Burgess, Sacramento, Calif.; Arthur L. Burks, San Francisco; George C. Burns, Compton, Calif.; Ivor MacIvor Campbell, Portland, Ore.; Roy Arnold Darke, Salt Lake City; Edward S. Dean, San Francisco; William T. Drysdale, Boise, Idaho; Robley N. Ellis, Agnew, Calif.; David J. Farber, San Francisco; Rush B. Faville, San Francisco; Milton H. Firestone, Los Angeles; Franklin H. Garrett, Norwalk, Calif.; Lorenz F. Gerlach, San Mateo, Calif.; Louise J. Gordy, Van Nuys, Calif.; Albert H. Held, Beverly Hills, Calif.; Keith D. Heuser, Denver; Sidney Z. Hulbert, North Hollywood, Calif.; Henry Hutchinson, Moose Lake, Minn.; Maurice Kaplan, San Francisco; Bernard S. Klauber, Memphis, Tenn.; Melvin K. Knight, Vancouver, Wash.; Irwin Kravetz, Huntington Park, Calif.; Jack Levitt, San Diego, Calif.; Frank A. Majka, Lincoln, Neb.; Solomon B. Meyerson, Honolulu, Oahu, T. H.; John Albert Mitchell, Patton, Calif.; David W. Morgan, Pasadena, Calif.; Carl V. Morrison, Portland, Ore.; Edwin P. Peterson, Boise, Idaho; Roger E. Phillips, Topeka, Kan.; Robert P. Quirmbach, Agnew, Calif.; Lewis A. Roberts,* Oakland, Calif.; Arthur D. Rosenthal, North Little Rock, Ark.; John F. Ryan, San Francisco; Lee F. Scarborough, Galveston, Texas; Henry Snyderman, Wadsworth, Kan.; Gerald W. Smith,* Houston, Texas; James Solomon, Los Angeles; Henry Spitzer, Santa Monica, Calif.; Samuel Susselman, San Francisco; Howard V. Turner, Palo Alto, Calif.; J. Ray Van Meter,* Palo Alto, Calif.; Henry J. Wegrocki, Los Angeles; Leon J. Whitsell,* San Francisco; Bruce A. M. Williamson, San Marino, Calif.; Emanuel Windholz, San Francisco.

Neurology.—Lindsay E. Beaton,* Tucson, Ariz.; Edison D. Fisher, Los Angeles; Lester H. Margolis, San Francisco; William F. Northrup, Pasadena, Calif.; John T. Robson, Tacoma, Wash.; Robert B. Sampliner,* Los Angeles; Emmanuel Silver,* Palo Alto, Calif.

MENTAL HYGIENE RESEARCH FELLOWSHIPS

In order to promote the development and interest of competent research workers in the field of mental health, the United States Public Health Service will award a limited number of mental hygiene research fellowships for graduate work in medical and related sciences, Oscar R. Ewing, Federal Security Administrator, announced today. These fellowships are open to psychiatrists, psychologists, social workers, anthropologists, sociologists and any other persons interested in research in the field of mental health who have the proper qualifications.

A predoctorate research fellowship is available to qualified applicants. For persons with a bachelor's degree the stipend is $1,200 a year, and $1,600 a year for those with dependents. For applicants with a master's degree, or its equivalent in graduate work, the stipend is $1,600, and $2,000 for those with dependents. Tuition for courses taken in connection with the fellowship will also be paid. These fellow-

* The asterisk denotes complementary certification.

ships are also granted to medical students who have completed one or two years of their medical course and who wish to spend one, two or three additional years in a basic science relating to mental health before completing their studies toward the degree of Doctor of Medicine.

A postdoctorate research fellowship is awarded to qualified persons holding a doctor's degree in medical or related fields. This fellowship carries a stipend of $3,000 per year for doctors without dependents and $3,600 per year for doctors with dependents. The stipend of postdoctorate fellowships which are renewed is increased $300 over the previous year. Tuition fees are not provided with this fellowship.

A special research fellowship is awarded to applicants who qualify for a postdoctorate fellowship and, in addition, have demonstrated outstanding ability or who possess specialized training for a specific problem. This fellowship does not carry a set stipend, the amount being determined in the individual case.

Applicants are required to file a statement outlining the investigation on which they will work.

Requests for application forms and additional information on research fellowships should be addressed to the Division of Research Grants and Fellowships, National Institute of Health, Bethesda 14, Md.

A new bimonthly periodical, *Fertility and Sterility*, sponsored by the American Society for the Study of Sterility, will make its appearance early in 1949. The journal will be devoted to original articles, reviews and abstracts on the clinical problems of sterility and impaired fertility.

The periodical will be published by Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, at $7.50 a year; foreign, $9.00.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

THE BRAIN IN A CASE OF HUMAN CYCLOPIA. OTTO MARBURG and FRANCIS J. WARNER, J. Nerv. & Ment. Dis. **103**:319 (April) 1946.

Marburg and Warner studied the microscopic features of the brain in a case of human cyclopia and compared their observations with those in the case of Marburg and Mettler. The brain stem as high as the diencephalon was normal except for the loss of cortical pathways. Although the optic nerves were present, there was no optic chiasm. A thick connective tissue membrane covered the floor of the third ventricle as far as the infundibular funnel. In the telencephalon, except in the occipital lobes, there was only one ventricular lumen. The olfactory bulbs and tracts and the striae olfactoriae were destroyed.

Destruction of the secondary olfactory systems is followed by absence of the peripheral olfactory apparatus. Subsequently, a change in the skeleton occurs, with development of a common orbit and one eye, or two eyes fused in the midline, as in this case. Preservation of the central olfactory system, the habenula, the mamillary bodies and the fornix is evidence of the independent development of these structures. The pathologic process leading to the production of such monsters involves the germ plate in the first four weeks of fetal development.

CHODOFF, Washington, D. C.

COLLAGEN CONTENT OF RABBIT SCIATIC NERVE DURING WALLERIAN DEGENERATION. M. ABERCROMBIE and M. L. JOHNSON, J. Neurol., Neurosurg. & Psychiat. **9**:113 (Oct.) 1946.

Abercrombie and Johnson investigated the amount of collagenization occurring in the nontraumatized part of the peripheral stump following injury as an index of the degree of return of function. Sciatic nerves of rabbits were used, either undegenerated or degenerated for periods of twenty-five, fifty, one hundred and two hundred days. The collagen content was determined by the chemical method of Lowry, Gilligan and Katersky. The results showed that a continuous increase in collagen occurs after degeneration, so that at the end of two hundred days the content of the nerve has doubled. At the end of each period of degeneration the mean collagen content was significantly higher than at the preceding period, though the increase during the first twenty-five days was not so well established. The authors found that 100 mg. of undegenerated nerve contains an average of 0.57 mg. of collagen nitrogen and that in the course of two hundred days of degeneration the nerve lays down on the average an additional 0.63 mg., the rate of collagen formation being nearly constant throughout the period of observation. The mean content of collagen protein is 3.2 per cent of the wet weight in undegenerated nerves. After twenty-five days of degeneration it has fallen to 2.4 per cent, but thereafter rises, reaching 6.2 per cent after degeneration for two hundred days. The destruction of nerve fibers during degeneration entails a large loss of residue nitrogen, the loss being complete by twenty-five days. The total nitrogen of the nerve, however, increases up to a period of degeneration of at least fifty days. The authors concluded that the process of collagenization is continuous over

a long period of degeneration. This collagen formation around shrunken Schwann tubes hinders expansion on reinnervation. This suggests that once the tubes have shrunken a delay in suture means a less favorable prospect, whereas after early suture the new collagen, even if not suppressed, forms with the expansion of the Schwann tubes and therefore tends to hinder much less the return to normal fiber diameters.

M. MALAMUD, San Francisco.

Physiology and Biochemistry

THE ESSENTIAL LESION IN EXPERIMENTAL DIABETES INSIPIDUS. P. HEINBECKER, H. L. WHITE and D. ROLF, Endocrinology **40**:104, 1947.

In this investigation, the authors confirmed their observations (1941) that diabetes insipidus can occur in the absence of the pars distalis of the hypophysis. They found that experimental diabetes insipidus in dogs follows destruction or denervation of the entire neurohypophysis. In dogs previously rendered polyuric through denervation of the neurohypophysis, subsequent removal of the pars distalis did not abolish the polyuria. Although the output remained above normal, the amount of urine excreted by these animals decreased strikingly over a twelve to an eighteen month period. Experimentally, the hypophysectomy must include all the supraoptic nuclei and about 50 per cent of the large cells of the paraventricular nuclei, particularly in the rostral portion. A residuum in dogs of 15 per cent of the cells of the supraoptic nuclei, in the absence of any of the pars distalis, will prevent any exhibition of increased output of urine.

The decrease in urinary output following removal of the pars distalis in hypophysectomized dogs may be attributed to a gradual atrophy of other endocrine glands, such as the adrenal cortex and thyroid, which are normally under the influence of the pars distalis.

The authors conclude that incomplete destruction or denervation of the neurohypophysis, including the median eminence, may prevent the development of diabetes insipidus in the absence of the pars distalis, whereas the presence of the pars distalis may permit the development of diabetes insipidus, even in the presence of a slight residuum of functional neurohypophysis.

FRANKEL, Philadelphia.

EFFECT OF DIETHYLSTILBESTROL ON THE ANTERIOR HYPOPHYSIS OF THYROIDECTOMIZED RATS. B. L. BAKER and N. B. EVERETT, Endocrinology **41**:144 (Aug.) 1947.

Baker and Everett attempted to determine whether estrogenic substances induced changes in the hypophysis directly or through the stimulation of thyroid activity. Changes in the acidophilic cells of the anterior lobe of the hypophysis, manifested by increases in size, number and accelerated mitotic activity, as well as increase in the weight of the hypophysis, were taken as the criteria of stimulation of the hypophysis. Small doses of diethylstilbestrol were injected daily into immature thyroidectomized rats for four days and into adult ovariectomized-thyroidectomized rats for ten days, with the production of changes in the acidophilic cells. Small doses of diethylstilbestrol and a short period of administration were used in order to prevent agranulation of the acidophils and their conversion into chromophobes. The authors conclude that the stimulating action of estrogen on the hypophysis is not mediated by the thyroid gland and that it may be elicited in adult, as well as in immature, rats.

FRANKEL, Philadelphia.

THE PROPRIOCEPTIVE NERVOUS SYSTEM. C. JUDSON HERRICK, J. Nerv. & Ment. Dis. **106**:355 (Sept.) 1947.

Sir Charles Sherrington classified the total action system into three classes of performance: exteroceptive, interoceptive and proprioceptive. Herrick regards the last system as ancillary to the other two and holds that this proprioceptive system is segregated from the other systems, not in terms of the sensory organs involved, but in its action in exerting regulatory control over the action of all skeletal musculature.

The author emphasizes Sherrington's concern with (1) the integration of the analytic processes of reflex in the interest of the welfare of the body as a whole and (2) the action of the nervous system, not the statics of structure. In line with Sherrington's concept of the cerebellum as the "head ganglion of the proprioceptive system," the researches of Larsell, Fulton, Dow and others have shown that the cerebellum is a union of two components: a lateral part, dominated by the vestibular system, and a median body, for the reception of the nonvestibular systems of afferent fibers. Physiologic experiments have demonstrated local representation in the cerebellum of different areas of skin, of vibrissae, of hearing, of vision and of the various synergistic muscles.

The author believes that proprioception includes more than the vestibular apparatus and the deep sensibilities, inasmuch as cerebellar function includes much more than proprioception as usually defined. He therefore defines proprioception in terms of the results achieved in facilitating the execution of muscular action, rather than in terms of the modalities of sense employed. "The proprioceptive system includes all peripheral end organs and nerves and all central adjustors in the spinal cord, brain stem, cerebellum, and cerebral hemispheres that collaborate in the coordination and synergizing of muscular activity in process."

It is suggested that the term proprioceptive system be replaced by another name, the proprius system, in order that the several components of behavior be kept intact as units of action and not dismembered by any artificial classification of the end organs employed.

FARMER, Philadelphia.

CEREBROSPINAL FLUID STUDIES IN CEREBRAL CONCUSSION. M. SPIEGEL-ADOLPH, H. T. WYCIS and E. A. SPIEGEL, J. Nerv. & Ment. Dis. **106**:359 (Sept.) 1947.

Forty-five cases of cerebral concussion, with loss of consciousness and without neurologic signs, were studied to determine the effect on the spectrophotometric properties of the spinal fluid. In 35 control cases, in which barbiturates were not used, the mean value of the extinction coefficient (E) at 2,650 angstroms was normal (1.24 ± 0.59), whereas the cerebrospinal fluid in most cases of cerebral concussion showed selective absorption between 2,550 and 2,750 angstroms, with a peak at 2,650 angstroms. In cases in which the interval between the accident and the lumbar puncture did not exceed two months, E was 2.47 ± 0.73, a statistically significant difference. In the cases in which examination was made from six months to three years after the accident, the mean value of E was 1.73 ± 0.28, approximating the value for normal subjects who were taking barbiturates (1.82 ± 0.66). In 7 cases of concussion multiple examinations revealed that the selective absorption power reached a maximum about the fifth day after injury and showed a pronounced decrease on the tenth to the eighteenth day.

The authors postulate the presence of cleavage products of nuclear substances in the cerebrospinal fluid as the probable cause of this selective absorption, for the

following reasons: 1. Purine and pyrimidine compounds yield similar absorption bands. 2. Chromatolysis has been found in various parts of the cerebrum at an early stage after concussion. 3. During chromatolysis after section of nerve roots, a decrease in the extinction coefficient of the cytoplasm of motoneurons and a change in the slope of the absorption curve indicate a greater loss of nucleotides than of proteins from the cells. The concentration of these substances in the cerebrospinal fluid more or less parallels the course of chromatolysis, suggesting that the presence of this selective absorption is the counterpart of the chromatolytic changes in the nerve cells.

In another series of experiments, enzymatic studies showed that normal cerebrospinal fluid split only small amounts of thymonucleic acid and seemed unable to split a definite amount of nucleic acid of plant origin, whereas cerebrospinal fluid obtained after concussion showed a more pronounced splitting ability for both animal and plant nucleic acids. The exact nature of these enzymes remains to be studied, but it is tentatively assumed that the enzymes of the deaminase type are responsible.

The authors suggest that spectrophotometry of the cerebrospinal fluid may be a valuable aid in providing objective data in cases of cerebral concussion.

FARMER, Philadelphia.

A NEW TYPE OF PSYCHOGALVANOMETER. JEAN HEUSKIN and JEAN BOBON, J. belge de neurol. et de psychiat. **47**:22 (Jan.) 1947.

Heuskin and Bobon describe a new type of psychogalvanometer which may be used for rapid determination of the electrical resistance of the skin. The response is registered photographically by means of an oscillograph. Oscillations with an audible frequency are registered on the film simultaneously with the period of excitation. A system of relays permits registration on the same film of the time and duration of application of the stimulus.

DEJONG, Ann Arbor, Mich.

EXPERIMENTAL COMPARISON OF CONVULSIVE SEIZURES DUE TO ELECTROSHOCK AND CORTICAL EPILEPSY. P. GLEY, M. LAPIPE, J. RONDEPIERRE, M. HORANDE and T. TOUCHARD, Rev. neurol. **77**:57 (March-April) 1945.

Convulsions were readily induced by electroshock in a dog after the motor cortex was excised and in a pigeon after removal of the cerebral hemispheres. In both cases sections of the cord showed degeneration of the pyramidal tracts; in the pigeon the anterior tracts were degenerated. The convulsive seizures were exactly similar to those seen in intact animals stimulated in the same way except that the amount of current required was slightly higher in the pigeon whose cortex had been removed. The threshold for cortical epilepsy (convulsions induced by direct stimulation of the cortex) is raised readily by diphenylhydantoin sodium. This drug has less effect on the threshold for electroshock convulsions. With adequate doses one can suppress experimental cortical epilepsy, whereas the same dose will have no effect on electroshock seizures. After section of both inferior cerebellar peduncles, typical electroshock convulsions were not induced in the dog. Cortical epilepsy can be produced in these animals. The authors conclude that electroshock brings into play an extrapyramidal mechanism. The studies confirm previous observations that tonic and clonic convulsions can result from excitation of cells below the cortex, even in the spinal cord (*Rev. neurol.* **75**:127, 1943).

N. SAVITSKY, New York.

CHANGES IN THE BLADDER IN DIABETES. C. A. CAMPOS and A. D. COLODRERO, Prensa méd. argent. **34**:1588 (Aug. 22) 1947.

Campos and Colodrero made cystometric studies on 26 diabetic patients. Twenty-four of the patients had an increased capacity, varying from 550 to 1,200 cc.; 3 of the patients had a capacity of 1,200 cc. Two patients with infections of the bladder had capacities of less than 550 cc. In only 6 patients did the cystometric study indicate the existence of a neurogenic bladder. Sixteen of the 26 patients showed residual capacities up to 1,000 cc., with an average of 200 cc. Only 4 of the patients with residual urine had atonia of the wall of the bladder. Eleven patients had diabetic polyneuritis. Two patients with distended bladders did not have polyneuritis, and 4 with distended bladders had polyneuritis. Three patients with polyneuropathy had no atonia, though distention was present. The authors believe that distention of the bladder occurs first, as a result of polyuria and weakness of the bladder wall due to the diabetes. Residual urine appears later. Polyneuritis plays a slight role in accounting for the changes in the bladder. The authors are inclined to believe that there is a direct effect on the muscles of the bladder during the course of diabetes. They prefer this theory to that of a neuropathy of the parasympathetic system, as suggested by Rundles.

N. SAVITSKY, New York.

Neuropathology

TOXIC-PRODUCTIVE ENCEPHALITIS. GEORGE B. HASSIN, J. Neuropath. & Exper. Neurol. **4**:354 (Oct.) 1945.

Hassin reports in detail 2 cases of toxic-productive (serous or toxic) encephalitis. He states that this type of encephalitis is of common occurrence but that the diagnosis is made only occasionally by the clinician or the neuropathologist. It should be noted that some authors are loath to recognize a toxic type of encephalitis, although such skeptics are at a loss to offer a more definite diagnosis. The disorder is frequent, not only in children but also in adults. It is often a manifestation of exclusive involvement of the central nervous system. Hassin states that productive or toxic-productive encephalitis is commoner than any other form of encephalitis.

From the observations presented, it is clear that the pathologic substratum of this form of encephalitis consists of mesodermal changes, in the form of capillary proliferation and the formation of new blood vessels. These changes are combined with parenchymatous alterations, infiltrations of the adventitia with hematogenous elements usually being absent. Productive encephalitis, like the infiltrative type, does not signify a specific disease process. It may be a manifestation of a primary cerebral disorder or of a systemic disease process. In nonfatal cases of toxic-productive encephalitis residual changes may persist severe enough to account for some abnormalities in behavior or for purely neurologic sequelae.

GUTTMAN, Philadelphia.

INTRASELLAR MENINGIOMA AND MULTIPLE CEREBRAL GLIOBLASTOMAS. WALTER R. KIRSCHBAUM, J. Neuropath. & Exper. Neurol. **4**:370 (Oct.) 1945.

Kirschbaum reports the case of a Negro woman who at the age of 19 had several periods in which she was excited and resistive and "had many complaints." During the subsequent fifteen years she became obese and had "occasional fainting spells." At the age of 35 she entered the hospital. She appeared tired and somewhat drowsy, and a diagnosis of mental deficiency without frank psychosis was

postulated. However, examination revealed bilateral papilledema, and a roentgenogram of the skull showed enlargement and ballooning of the sella turcica with erosive changes of the dorsum, suggesting a tumor of the pituitary gland. After several weeks the patient became quieter and better adjusted to the institutional regimen. Her vision deteriorated in the course of the next few months, and "epileptiform seizures set in." The patient died suddenly, about a year after her final admission.

Postmortem examination disclosed multiple gliogenous tumors in various stages of development. Certain portions of the pontocerebellar tumor, the structure of which resembled medulloblastoma, suggested ontogenetic disturbances. Numerous, smaller gliogenous tumors projected into the lateral ventricles and were stated to have a similar basis. There was a similarity in appearance between the periventricular nodules and the small tumors arising from the head of the caudate and thalamic nuclei in cases of tuberous sclerosis. However, the histologic features were by no means those encountered with atypical periventricular sclerosis. These gliomas occurred with an intrasellar meningioma in connection with the pituitary body. Kirschbaum postulates histogenetic disturbances of various germinal structures in the neuraxis.

GUTTMAN, Philadelphia.

CEREBRAL CHANGES ASSOCIATED WITH SENILITY. P. DIVRY, J. belge de neurol. et de psychiat. **47**:65 (Feb.) 1947.

The aging process and death have always constituted an enigma for the human mind. Divry expresses the belief that the study of the senile brain gives information in favor of a colloidal concept of the aging process. He states that the cerebral substance can perhaps be considered a colloidal solution. The cerebral degeneration of senility, which is characterized by the fibrillary changes of Alzheimer, senile plaques and glial hyperplasia, is a result not so much of pathoanatomic alterations as of histochemical changes which produce degeneration of the cerebral tissues, especially of the protein constituents. This concept affords a fertile basis for the understanding of cerebral degeneration and permits a new understanding of the process of aging.

DEJONG, Ann Arbor, Mich.

HISTOPATHOLOGIC STUDIES AND PROBLEMS OF DISEASES OF THE WHITE MATTER. LUDO VAN BOGAERT, J. belge de neurol. et de psychiat. **47**:82 (Feb.) 1947.

Van Bogaert reviews many of the current theories that have been proposed to explain diseases of the white matter but finds that none of them adequately accounts for the total picture seen in multiple sclerosis and related disorders. He expresses the belief that vascular thromboses and other circulatory disturbances are usually followed by the development of necrosis and severe degenerative changes with or without diapedesis of erythrocytes and without specific demyelination; the lesions do not closely resemble those seen in multiple sclerosis. Van Bogaert has observed vascular lesions of this type with capillary necrosis in toxic and infectious states. The histopathologic changes associated with carbon monoxide and trauma resemble those seen in cases of subacute hemorrhagic leukoencephalitis; there is usually edema, with some inflammatory reaction. Other toxic conditions are characterized principally by edema, sometimes with secondary ischemia.

Recent research has dealt with the production of changes in the nervous system by means of antigenic substances. Van Bogaert believes that allergic and anaphylactic reactions may cause some forms of demyelination, but states that it is impossible to reproduce experimentally by allergic phenomena a demyelinating lesion which histologically resembles perivenous or disseminated sclerosis.

Certain myelinotic substances produce changes which most closely resemble those of multiple sclerosis, and van Bogaert believes that physicochemical studies, rather than histopathologic ones, will be most important in the further investigation of multiple sclerosis. He believes that an hereditary background which leads to breakdown of neural tissues and related metabolic alterations is important.

DEJONG, Ann Arbor, Mich.

Psychiatry and Psychopathology

SEVEN YEAR SURVEY OF INSULIN TREATMENT IN SCHIZOPHRENIA. ALEXANDER GRALNICK, Am. J. Psychiat. **101**:449 (Jan.) 1945.

Gralnick made a seven year survey of 554 patients with schizophrenia treated with insulin. He concluded that this type of therapy produces quicker remissions and has worth while results in cases of schizophrenia of one or two, and possibly of three, years' duration. Regardless of the age and type of schizophrenia, 73 per cent of the patients who had been paroled six years returned to the hospital. There was no definite correlation between the results obtained and the number of treatments given or the comas induced. Gralnick concludes that if there is no definite improvement after twenty-five or thirty treatments and one-half that number of comas the patient will not become well enough to be paroled. He upholds the belief that patients whose illness is of short duration do well, for they are close to reality and are able to respond to the treatment situation, whereas the patients with a long illness are withdrawn and psychologically fixed.

BORKOWSKI, Boston.

CLINICAL OBSERVATIONS ON STARVATION EDEMA, SERUM PROTEIN AND EFFECT OF FORCED FEEDING IN ANOREXIA NERVOSA. J. M. BERKMAN, J. F. WEIR and E. J. KEPLER, Gastroenterology **9**:357 (Oct.) 1947.

Berkman, Weir and Kepler point out that during and after World War I it was observed that starvation often was followed by edema and that in about half the subjects the concentration of the serum proteins was decreased. It also was observed that in apparently identical circumstances normal values for serum proteins might be obtained and that definitely subnormal values were not necessarily associated with edema. Possibly because the observations first mentioned were more in keeping with Starling's theory of formation of edema, emphasis was placed on the importance of the serum proteins in maintaining a dynamic equilibrium between the intravascular and interstitial fluids. During and after World War II emphasis was placed on the absence of correlation between starvation edema and the concentration of serum proteins. Starling's concepts were scrutinized and sometimes discredited. The authors were interested in the manner in which patients who were emaciated as a result of anorexia nervosa gained weight. Thirty-one patients with anorexia nervosa were studied at the Mayo Clinic, with particular attention to the weight curve during dietary treatment, the occurrence of edema and its relation to the weight curve and the relation of the edema to the concentration of serum protein. No pitting edema was observed at any time in 15 patients, while in 12 patients edema was present on admission. Four patients acquired edema during treatment, and in 6 patients preexistent edema was increased after treatment. Among the patients who recovered from emaciation and may never have exhibited edema, the character of the weight curve suggested that a sequence of events occurred which was identical with that which occurred in patients who did exhibit edema. In the treatment of anorexia nervosa three phases can often be seen in the weight curve. In the first phase edema may occur, or if present it may be increased.

In the second phase edema may persist or slowly decrease while the patient gains flesh. The weight of water lost is approximately equal to the weight of the flesh gained. In the third phase the disturbance in water balance has been corrected, waterlogging has been overcome and a progressive gain in weight occurs. The weight curve may be misleading in evaluating the actual storage of flesh. In severe cases of untreated anorexia nervosa values for the serum proteins more often than not were within the normal range. In about a third of the cases values lower than normal were encountered. The level of the serum protein usually could not be correlated with the presence of edema. With treatment, the concentration of serum protein may decrease temporarily, possibly because of hemodilution.

J. A. M. A.

PERSONALITY AND PSYCHOSOMATIC DISTURBANCES IN PATIENTS ON MEDICAL AND SURGICAL WARDS. BELA MITTELMANN, ARTHUR WEIDER, KEEVE BRODMAN, DAVID WECHSLER and HAROLD G. WOLFF, Psychosom. Med. **7**:220 (July) 1945.

The authors believe that disorders of personality and psychosomatic disturbances in association with infection and trauma may influence the rate and degree of recovery. They made a survey of the incidence of such disturbances in 450 patients in medical and surgical wards. Of this series, 45, or 10 per cent, had severe or moderately severe personality disturbances, and 90, or 20 per cent, had mild personality disturbances.

Thirty per cent of the patients with personality disorders had a preexisting personality defect, which was aggravated by infection or trauma. In 37 per cent personality disturbances were precipitated by, or first became evident in association with, infection and trauma. Twenty per cent had personality disturbances with serious defects in structure or function; this group includes patients with psychosomatic disturbances, such as hypertension, which may be associated with structural defects. Personality disturbances in patients without gross structural defect, but with excessive complaints and disturbance of function, occurred in 8 per cent, whereas 4 per cent had trauma resulting from a personality disturbance.

The authors found that the patients' difficulties arose in connection with the threat to bodily safety, frustration of dependency needs, hostility, sexual problems and the failure to live up to high standards of achievement. All the patients had conflict between group ideals and a desire for protection. In some instances the patient was aware of it; in others he was not. In psychopathic persons feelings of frustration and guilt expressed themselves in diffuse hostility and defiance of accepted social ideals.

WERMUTH, Philadelphia.

AN HYPNOTIC ABLATION TECHNIQUE FOR THE STUDY OF PERSONALITY DEVELOPMENT. HERBERT SPIEGEL, JOEL SHOR and SIDNEY FISHMAN, Psychosom. Med. **7**:273 (Sept.) 1945.

Spiegel, Shor and Fishman made a systematic investigation into the precise character of hypnotic regressed states by "placing" the subject at arbitrarily suggested periods in his life history and then having him perform a series of standard psychologic tests. These tests included the Revised Stanford-Binet Intelligence Test, Koh's Block Performance Tests, the Rorschach test, studies of conditioned reflexes and electroencephalographic examinations. The tests were administered by a third person, who had had no hypnotic influence on the subject.

The results showed that with this technic there occurs a blocking out or ablation of all development of personality from the present back to the specified day. Thus, each age level may be studied for the quality and degree of integration of the subject's capacities for adaptation.

WERMUTH, Philadelphia.

THE STRESS TOLERANCE TEST: PRELIMINARY EXPERIMENTS WITH A NEW PROJECTIVE TECHNIQUE, UTILIZING BOTH MEANINGFUL AND MEANINGLESS STIMULI. M. R. HARROWER and ROY R. GRINKER, Psychosom. Med. **8**:3 (Jan.-Feb.) 1946.

Harrower and Grinker devised the stress tolerance test in order to assess the capacity of a subject's ego to master anxiety. The subject was first given five of the Rorschach ink blot series; he was then shown ten dramatic war and combat pictures and asked to write down the first thing to enter his mind. This was followed by five of the Harrower ink blot series.

The authors applied the test to patients with operational fatigue who were under treatment at an army convalescent hospital, as well as to a control group. Various criteria were found to be important in determining whether a patient was disturbed: failure in either ink blot series; poorer performance in the second ink blot series; failure in description of the war pictures; evasion, univerbal answers, personalization or expression of feelings to the war pictures.

The test proved valuable when used as an objective measure of the degree of the patient's improvement.

WERMUTH, Philadelphia.

A STUDY OF CONDITIONED VASOMOTOR RESPONSES IN TEN HUMAN SUBJECTS. LOUIS A. GOTTSCHALK, Psychosom. Med. **8**:16 (Jan.-Feb.) 1946.

Gottschalk produced positive conditioned vasomotor responses in 4 of 10 human subjects. A faradic current was used as the unconditioned stimulus, and the vascular reactions were measured by means of the photoelectric plethysmograph. The resulting conditioning and extinction curves did not always follow the typical curves of learning and forgetting.

Three subjects who manifested signs and symptoms of imbalance of the autonomic nervous system were more easily conditioned than other subjects. Subjects who were relatively easily conditioned showed more rapid and complete elimination of incidental vascular reflexes to the light stimulus and showed a tendency toward more stable conditioned responses during extinction than did subjects who were not easily conditioned.

The author found that the intensity of sensations as reported by a subject was not a valid indication of the magnitude of the physiologic vascular reactions concomitant with these sensations.

WERMUTH, Philadelphia.

"POPULAR" RESPONSES AND CULTURAL DIFFERENCES: AN ANALYSIS BASED ON FREQUENCIES IN A GROUP OF AMERICAN INDIAN SUBJECTS. A. IRVING HALLOWELL, Rorschach Research Exchange **9**:153 (Dec.) 1945.

Hallowell analyzed the locale, content and frequency of 3,684 Rorschach responses given by a group of 151 American Indian subjects, ranging in age from 6 to about 75 years. He compared them with lists of "popular" responses obtained by other authors and concluded that "for the purpose of cross-cultural comparisons popular responses fall into three major categories": (1) universal, (2) common and (3) unique. In the first category are a few responses which are the most

frequent in a large number of distinct cultural groups. The second category contains those responses which vary widely in frequency and in order of rank in the total series of popular responses for various groups. The popular responses in the third category are characteristic of a single cultural group. Illustrative examples are tentatively placed in this category. MARCOVITZ, Philadelphia.

Diseases of the Brain

ATROPHY OF THE OPTIC NERVE FOLLOWING HEMORRHAGE. PAUL LEVATIN, Arch. Ophth. **37**:18 (Jan.) 1947.

Amblyopia following acute loss of blood is an old, but relatively rare, disease. An average of 1 case a year has been reported in the world's literature of the past twenty-five years. Vail saw only 4 cases of such visual loss in his vast experience in military ophthalmology in Europe in World War II. The author discusses in part the history of this uncommon condition, at the same time bringing up to date the literature from 1901 to the present. Various theories have been presented for the loss of vision following distant hemorrhages. It is certain that some factor other than ischemia is responsible for the atrophy of the optic nerve.

In the case reported by Levatin the optic nerve atrophy resulted from massive hemorrhage due to a ruptured duodenal ulcer in a man aged 34. The atrophy occurred almost immediately in one eye and developed somewhat later in the opposite eye, and was associated with persistent circulatory failure with profound anemia.

SPAETH, Philadelphia.

EXOPHTHALMOS AND ASSOCIATED OCULAR DISTURBANCES IN HYPERTHYROIDISM. ISADORE GIVNER, MAURICE BRUGER and OTTO LOWENSTEIN, Arch. Ophth. **37**:211 (Feb.) 1947.

When Marine and his associates (Marine, D., and Rosen, S. H.: *Proc. Soc. Exper. Biol. & Med.* **30**:901 [April] 1933) produced bilateral chronic progressive exophthalmos by daily muscular injections of 0.05 to 0.1 cc. of methyl cyanide in 2 to 3 month old rabbits maintained on a diet of alfalfa, hay and oats, they came to the following conclusion: "Cyanides appear to act by inhibiting metabolic processes. This inhibition stimulates the hypothalamic centers, which in turn, stimulate the pituitary to produce the thyrotropic hormone, which in turn stimulates the thyroid gland and independently the sympathetic centers in the mid-brain, causing exophthalmos."

The authors reasoned that, since pupillography could show evidences of central sympathetic disturbances, it might be advantageous to determine the nature of these changes in hyperthyroidism. Their pupillographic studies in 21 cases of hyperthyroidism revealed a redilation block. This block is ascribed to a hypothalamic origin and lends the first tangible evidence to the confirmation of Marine's hypothesis.

In the study of their cases, the authors also concluded that if vision is impaired because of involvement of the optic nerve in patients with thyrotropic exophthalmos complete uncapping of the optic foramen should be included in the decompression.

The evidence accumulated supports the contention that the immediate cause of exophthalmos, whether it be of the thyrotoxic or the thyrotropic type, resides in the extraocular and smooth muscles of the eyeball, Tenon's capsule and the eyelid. In the case of thyrotoxic exophthalmos, it is essential to know whether, in addition to removal of the sympatheticotonia and the lowering of the thyroxin content of the blood, it is possible to cause reversal of flabbiness of the muscles.

In the case of thyrotropic exophthalmos, the question arises whether round cell infiltration and fibrosis can be lessened. All medication attempted by the authors seemed of no avail. To offset the pessimistic view that exophthalmos once established will not recede, it should be noted that exophthalmos has been reversed in some cases by the administration of iodine and during pregnancy. The administration of iodine orally for several months reduced the exophthalmos in 3 patients, as demonstrated on the exophthalmometer.

SPAETH, Philadelphia.

CEREBELLAR SUBDURAL HYDROMA: REPORT OF ACUTE CASE FOLLOWING HEAD INJURY. W. T. GRANT, Bull. Los Angeles Neurol. Soc. **11**:164 (Sept.-Dec.) 1946.

In the case reported by Grant, acute symptoms of right-sided cerebellar disturbance and of high intracranial pressure developed a few days after a head injury. Burr holes over the right cerebellar hemisphere and right parietal lobe liberated a subdural hydroma in both places. Symptoms subsided within a week, and the patient made a good recovery.

J. A. M. A.

CHRONIC CHOREA AND HYPERTONIC PARALYSIS OF GAZE. M. J. DEREUX, Rev. neurol. **77**:207 (July-Aug.) 1945.

Two patients with chronic chorea had immobile eyeballs and were unable to move the eyes voluntarily in any direction. Both patients, on turning the head to the right, were able to move the eyes in that direction; the eyes were moved slowly, as though overcoming resistance. When the head was moved to the right, the eyes remained toward the left, indicating intactness of reflex lateral conjugate gaze with movement of the head. In 1 case the injection of scopolamine hydrobromide, 0.25 mg., was followed by ability to move the eyes voluntarily in all directions.

N. SAVITSKY, New York.

VISUAL AGNOSIA, HEMIANOPSIA, ALEXIA, AGRAPHIA AND ANOMIA IN A CASE OF HEAD TRAUMA. H. VALLADARES and E. D. ROCCA, Arch. de neurocir. **2**:61, 1945.

A man aged 39 had been able to read and write prior to a severe injury to the occipital region, which resulted in loss of consciousness for fifteen days. He was disoriented and complained of severe impairment of vision. The neurologic examination soon after he regained consciousness showed large scars in the occipital region. The fundi were normal. The injury was followed by anterograde and retrograde amnesia, difficulty with thinking, inability to do simple problems, anomia, alexia and agraphia. There were right homonymous hemianopsia, which was especially prominent in the inferior quadrant, difficulty in localization of objects in space and evident impairment of depth perception. If a fixed object was moved, the patient found it difficult to localize it. He was able to differentiate intensities of light but could not distinguish colors. He showed the Lissauer form of visual agnosia. There were no hallucinatory experiences. Pneumoencephalographic examination showed mild hydrocephalus with dilatation of the ventricles and of the basal cisterns. At operation, on February 8, the left occipital lobe was exposed. Fractures of the skull were found in the left occipital region. The left occipital lobe was slightly pale, with firm leptomeningeal adhesions to the brain in that region. The vessels in the meninges did not pulsate but began to do so when small hygromas in the exposed region were evacuated. No lesion was observed in the medial aspect of the occipital lobe. Pronounced improvement in the visual agnosia

and other impaired functions were noted after the operation. All the findings could be explained by the presence of traumatic lesions in areas 18, 19 and 39 of Brodmann.

N. SAVITSKY, New York.

Muscular System

BACKACHE AND FIBROSITIS. W. R. CAVEN, Canad. M. A. J. **57**:37 (July) 1947.

According to Caven, fibrositis is the name given to a condition that produces small nodules in the connective tissue in certain susceptible persons; these nodules are sometimes painful or may give rise to referred pain or may be only tender to the touch. Fibrositis is probably the commonest cause of pain in the large group of persons with so-called rheumatic conditions. Some authors speak of fibrositic nodules, and others, mostly English, of rheumatic nodules. In the English literature fibrositis is usually grouped with rheumatic conditions, with which are also included various types of arthritis. The author thinks that fibrositis should be distinguished from these conditions, as there is no evidence of infection. The predisposing causes have been listed as sudden strain, wear and tear, chill, worry, poor posture and lack of use of certain groups of muscles. The essential pathologic process of fibrositis is now well known, as Stockman has described the changes in the white fibrous tissue of the muscles, nerves and fascia as being due to edema with serofibrinous exudation; in this exudate the fibroblasts proliferate rapidly, numerous minute new blood vessels appear and the whole forms a soft, ill defined, congested small swelling. The author regards fibrositis as one of the commonest causes of backache and of pains referred to the back. With fibrositis there usually exists some muscle spasm. Physical therapy is most important in the treatment. In the acute case with sudden onset, heat and rest with the use of analgesic drugs may be necessary for the first few days, before massage can be used. In the more chronic cases manipulation and deep massage can be used from the start. The essential part of treatment is to stretch the tissues involved, by some means or other, either by traction, when that is possible, or by firm massage directly on the tender nodules. Before any manipulative treatment is undertaken, it is wise to have roentgenograms made of the spine to rule out abnormal conditions of bone. The author describes manipulations to be carried out by the physician and exercises to be done by the patient.

J. A. M. A.

Experimental Pathology

PAGET'S DISEASE OF THE ATLAS AND AXIS. NORMAN WHALLEY, J. Neurol., Neurosurg. & Psychiat. **9**:84 (July) 1946.

Whalley reports the case of a man aged 66 in whom, over a five year period, there developed kyphosis of the upper cervical region associated with progressive weakness of the extremities and difficulty in micturition. Examination revealed forward dislocation of the head on the cervical portion of the spine, where a hard, bony mass was palpable. Neurologic examination revealed limitation of motion of the head and neck, spastic quadriplegia, paralysis of the muscles of the trunk and a sensory level 1 inch (2.5 cm.) below the clavicles. Roentgenologic examination revealed massive new bone formation, fusion of vertebrae, kyphosis and dislocation of the head, with narrowing of the spinal canal, and generalized signs of Paget's disease (osteitis deformans). There was histologic evidence of Paget's disease involving the atlas and axis, with demyelination of both crossed pyramidal tracts and, to a less extent, of the tracts of Goll and Burdach.

N. MALAMUD, San Francisco.

Encephalography, Ventriculography, Roentgenography

FIBROUS DYSPLASIA OF THE SKULL: A PROBABLE EXPLANATION OF LEONTIASIS OSSEA. DAVID G. PUGH, Radiology **44**:548 (June) 1945.

Fibrous dysplasia is a developmental anomaly having its onset in childhood. When more than one bone is involved, there is a tendency for the lesions to be predominantly unilateral, but often there is extensive bilateral involvement. Much of the pain, disability and deformity is due to pathologic fracture. Progress of the bony lesions after maturity is extremely slow or absent. Histologically, the medullary cavity is filled with a fibrous tissue, containing newly formed trabeculae of immature bone.

When pigmentation or endocrine disturbances are present, the condition is known as Albright's disease (polyostotic fibrous dysplasia).

The skull is involved in the majority of cases. The lesions involving the vault, the occiput and the mandible closely resemble roentgenologically the lesions of the long bones; that is, they consist in expansion of bone, with sclerotic and pseudocystic areas. The lesions in the frontal, sphenoid, ethmoid and maxillary bones are different, consisting of dense, sclerotic and thickened bone. Often, the paranasal sinuses are obliterated. The changes are those described in cases of leontiasis ossea.

In a review of 10 cases of leontiasis seen in the past five years at the Mayo Clinic, the author found that roentgenographic examinations of the long bones and pelvis had been made in only 3. Roentgenograms of the skull in the 10 cases of leontiasis and in the 5 cases of fibrous dysplasia showed similar changes.

The author concludes that in most cases leontiasis ossea is due to fibrous dysplasia of the skull. Probably other bones would be found involved if complete roentgenographic examination of the skeleton were made. The lesions, however, may be limited to the skull (localized fibrous dysplasia).

TEPLICK. Washington, D. C.

VALUE OF PNEUMOENCEPHALOGRAPHY IN CASES OF ACUTE HEAD INJURY. JULIO A. GHERSI, Prensa méd. argent. **32**:1537 (Aug.) 1945.

De Martel was the first to inject air into the subarachnoid space in cases of acute head injury. Ghersi reports 50 cases studied by means of pneumoencephalography. Air in the intracranial cavity in traumatic cases is not absorbed more quickly than in cases of other types. Pneumoencephalographic examination soon after the injury, followed later by another insufflation of air, showed a definite change, with collapse of one ventricle at first and later dilatation, indicating probable edema of the brain soon after the accident. At times extracerebral hemorrhage can be detected as a result of displacement of the ventricular system. Recurrent hemorrhages were noted in 1 case as a result of serial photographs taken after insufflation of air. The author also reports decidedly beneficial effects of pneumoencephalography in cases of acute head injuries. The intensity of complaints diminished, and the post-traumatic syndromes cleared up more rapidly. In 1 case he noted immediate disappearance of intense agitation. In 4 cases clouded states cleared up after the procedure. In 1 case Cheyne-Stokes breathing disappeared soon after the injection of air. The value of pneumoencephalography as objective evidence of cerebral damage is stressed.

N. SAVITSKY, New York.

Society Transactions

*CHICAGO NEUROLOGICAL SOCIETY

Joseph A. Luhan, M.D., Vice President, in the Chair

Regular Meeting, Oct. 8, 1946

Transplantation of Autogenous Nerve Graft in a Major Nerve Trunk.

DR. I. JOSHUA SPEIGEL.

On Aug. 28, 1944, the patient was struck by a machine gun bullet at the junction of the middle and the lower third of the thigh. He had immediate complete paralysis of the entire sciatic nerve. On October 26, an end to end anastomosis of the severed ends of the sciatic nerve was performed. Because there was no recovery of function or distal advance of the Tinel sign, a roentgenogram was taken, which revealed separation of the tantalum sutures. At reoperation a defect of 14 cm. was observed between the nerve ends. In spite of mobilization of the nerve to the sciatic notch and to the head of the fibula, hyperextension of the hip and acute flexion of the knee, the nerve ends could not be approximated. The distal portion of the common peroneal nerve was therefore resected over a distance of 14 cm. and the graft sutured between the proximal and the distal end of the tibial nerve with tantalum wire.

Examination on Aug. 25, 1946 revealed advance of the Tinel sign to 1 cm. below the ankle and 3 plus voluntary motor function in the soleus muscle and the inner and outer heads of the gastrocnemius muscle.

It is felt, therefore, that the autogenous nerve graft offers hope to those patients with irrevocable lesions of the sciatic nerve who previously were condemned to a lifetime of complete paralysis of this nerve, and occasionally even amputation.

DISCUSSION

DR. GEORGE PERRET: I enjoyed this presentation and was impressed by the return of function in this case. I should like to mention a similar case which I had several years ago, that of a man with a combined injury to the median and the ulnar nerve. Seven centimeters of the ulnar nerve was transplanted into the median nerve as an autogenous graft. One year later he could flex his index finger and thumb and had perfect sensation over the palmar surface of the tip of the finger. However, in most cases autogenous grafts are not available, and homogenous grafts are more easily obtainable for the repair of large nerve defects. My colleagues and I have transplanted homogenous nerve grafts in 5 patients: in 1, a graft 18 cm. long in the sciatic nerve; in 3, grafts 15, 14.5 and 11.5 cm. long, respectively, in the peroneal portion of the sciatic nerve; and in 1, a graft of 8 cm. in the posterior tibial nerve. The last patient, when examined ten years later, had normal function in the foot, and in 1 of the patients with a peroneal graft clinical, electrical and electromyographic examinations revealed beginning return of function eighteen months after operation. The other 3 patients were operated on within the last year. They have not as yet shown any signs of recovery, but reexploration of the wounds four to six months after transplantation revealed that the grafts had the appearance and consistency of normal nerves. (slides) They should give satisfactory results after sufficient time has elapsed.

DR. L. J. POLLOCK: I am happy that neurosurgeons have overcome the conviction that such grafts are not successful; since they are successful in animals, I

see no reason that they should not be so in man. I do not believe that a sufficient number of transplantations have been made, or that sufficient time has elapsed, to determine whether they are finally successful.

In defense of the older men in the first world war, it may be said that in no case of lesion of the sciatic nerve which I have seen would one have contemplated amputation. As a matter of fact, complete paralysis of the sciatic nerve is far less disabling than a lesion of the external popliteal nerve. With complete section of the sciatic nerve, only an arthrodesis of the ankle need be done, and the patient has no trouble.

DR. I. JOSHUA SPEIGEL: I was much interested in Dr. Perret's presentation. The problem of homogenous grafts was studied at Walter Reed General Hospital, where an unlimited supply of material for grafts was available. Woodhall and associates, in presenting their results, did not report any recoveries in a fairly large series, in which they used various nerves and a uniform, careful technic. It is possible that the patients could have been studied longer; the longest period of observation, I believe, was six months. I feel, therefore, that the results Dr. Perret has presented here should be brought to the attention of surgeons and neurologists.

In answer to Dr. Pollock, it is difficult for me to accept the statement that complete paralysis of the sciatic nerve is preferable to paralysis of the common peroneal nerve alone. A much smaller brace is necessary with the latter. In addition, anesthesia of the sole of the foot, with or without the careful attention of the patient, may result in trophic changes. I have seen these changes so severe and incapacitating that the thought of amputation and prosthesis was not at all as fantastic as might appear at first thought. I should like to make it clear, however, that I am not advocating amputation in cases of irrevocable paralysis of the sciatic nerve; on the contrary, I feel that results such as those described in this paper, and as those mentioned by Dr. Perret, militate strongly against it.

Electroencephalographic Indications of Cortical and Subcortical Activity.
DR. CHESTER W. DARROW.

Use of a twelve channel electroencephalographic equipment permitting exploration of an entire hemisphere by means of simultaneous monopolar and bipolar records from the same electrodes has called attention to important functional differences between monopolar and bipolar records. Monopolar electroencephalographic records (from the lead to the ear lobes) may be determined as much by activity adjacent to the indifferent electrodes as by activity in the cortex, as shown by simultaneous monopolar and bipolar records in a case of 3 per second petit mal activity. Synchrony of patterns from monopolar leads and nonsynchronous temporal and spatial progression of changes from bipolar connections on the scalp suggest monopolar and bipolar differentiation of cortical and subcortical factors. The synchronous monopolar patterns suggest a probable origin of outstanding features as an area not far from the common monopolar lead on the ears, whereas the temporally progressive bipolar changes suggest possible origin in the cortex; this is further shown by anatomic relations.

Records of simultaneous monopolar and bipolar changes during arousal from sleep show alpha and slower activity to be momentarily increased in both leads. Low voltage, fast activity in frontal-motor bipolar leads appears in the record only in those cases in which it is accompanied with clear palmar galvanic response. Fast activity typically begins during the latent period of the galvanic change. This suggests that excitation of the frontal and motor cortex may spread to sympathetic

centers and then discharge peripherally to produce autonomic effects. Peripherally induced autonomic changes may then feed back into the cortex and produce bursts of increased alpha activity, terminating the state of excitation.

Effects of hyperventilation on monopolar and bipolar patterns suggest that conditions impairing cortical function may increase bipolar (cortical?) susceptibility to subcortically initiated slow activity. Bipolar slow waves, typical of the brain of young children, suggest possible differences of development of phylogenetically older and younger portions of the nervous system; the great susceptibility of the child's brain to effects of hyperventilation is also consistent with such an explanation.

DISCUSSION

DR. GERHARDT VON BONIN: The cortex apparently is a mechanism not only for driving but also for suppressing or inhibiting. One might point to Magoun's work on the facilitatory and inhibitory center in the brain stem and to Coghill's statements concerning the phylogenetic aspect of cortical function. In lower vertebrates, such as the newts, the spinal cord generally functions as a whole, but in mammals its activity is differentiated into many partial patterns. Thus, as one ascends the phylogenetic scale, suppressing of "total" activity by the cortex, rather than driving it, is an important aspect of cerebral evolution. Such ideas receive additional support from Dr. Darrow's beautiful work.

Etiologic Factors in Experimental Neurosis from the Standpoint of Behavior. DR. GEORGE K. YACORZYNSKI.

Five modifications in the experimental setup were introduced to determine the conditions which are necessary to produce experimental neurosis in cats. Punishment consisted of mechanical pressure, electric shock and air blast. In some experiments the animals were either punished after they had learned to solve a problem or exposed to the electric shock and air blast without any means of escape. The results indicated that the only condition necessary to produce experimental neurosis is to have the animal emotionally disturbed for long periods. The generally accepted belief that a conflict, in the sense of frustration of an acquired or innate drive, is necessary to produce experimental neurosis is not substantiated by these results. Such a conflict is a sufficient, but not necessary, condition for the development of experimental neurosis. Evidently, the prolonged emotional disturbance with the concomitant physiologic changes can produce permanent effects on the animals whose symptoms have been placed in the category of experimental neurosis.

DISCUSSION

DR. WARD C. HALSTEAD: Dr. Yacorzynski has made a commendable attempt to start his experiments with a homogeneous population of animals. From the experimental procedures apparently two types of animals emerge: (*a*) a small group in which "experimental neuroses" were induced and (*b*) a larger group which were resistant to "experimental neuroses." To what extent was the latter group normal throughout, as reflected, for example, in the estrus cycle and in other physiologic functions? Were such functions altered in the "neurosis-susceptible" group?

DR. GEORGE K. YACORZYNSKI: Difficulty may exist with regard to the very definition of experimental neurosis. I think of this condition as the atypical behavior produced in animals exposed to a situation of stress or conflict. But to this I would add that the atypical behavior must last for a long period and be

generalized to include many situations. If an animal is disturbed only when placed in the training situation in which he has been punished, the condition may then be likened to a specific learned fear response or a phobia. It is possible, of course, that similar mechanisms are responsible for the establishment of a phobia and of the atypical behavior described as experimental neurosis. The possibility also exists that there are various degrees of experimental neurosis, but our data do not at present favor this opinion. Another question that may invite discussion is the definition of a conflict. Ordinarily, this term has been used to mean the frustration of a motive, the term "motive" including any learned act performed to satisfy the needs of the organism. Certainly, agreement on definitions is important; but, in the final analysis, only laboratory studies will clarify the whole field of the experimental neurosis.

So far as our observations were concerned, the control group raised in the laboratory displayed none of the atypical symptoms shown by the animals who became experimentally neurotic. Since the habitat of the former had been the laboratory from birth, the artificial living conditions of the laboratory appeared to have no effect on their behavior. Such animals could be bred and would raise a litter of young. From this evidence, therefore, one cannot say that the estrus cycle is disturbed. The behavior of the susceptible animals was also normal prior to the inducement of experimental neurosis. If experimental neurosis was induced, abnormal behavior was generalized to include many diverse forms of unusual behavior appearing in different situations. No conclusive evidence exists as to whether the estrus cycle is disturbed in such animals. The only observation I have from my studies is that a female refused to copulate with a male at the time the keeper considered the animal to be in heat. However, no vaginal smears were taken to determine whether this was during the animal's estrus cycle.

Electromyographic Studies on Cats After Section and Suture of the Sciatic Nerve. JAMES G. GOLSETH and DR. JAMES A. FIZZELL.

In this investigation, electromyographic data were obtained from the tibialis anticus muscles of 6 cats after section and immediate suture of the left sciatic nerve high in the thigh.

The electromyographic apparatus consisted of a three stage, push-pull preamplifier; a cathode ray oscilloscope; a power amplifier, and a loud speaker. The three electrodes required to make contact with the cat were (1) an electrocardiograph plate ground electrode, (2) a copper strip indifferent electrode and (3) a "vinylite"-insulated needle electrode, which was inserted into four chosen areas of the given muscle according to a sampling scheme.

One-half hour before each examination the designated animal was placed in a cloth sleeve with only its head and left lower extremity exposed. The foot, leg and thigh were clipped close before the electrodes were applied. Examinations were made on definite, predetermined days, from the eighth to the postoperative ninetieth day.

Electromyographic responses were of the following kinds: (1) no voltage response; (2) voltages from denervated voluntary muscle; (3) voltages from neurotized voluntary muscle and (4) voltages from normal voluntary muscle. (A slide was projected to show the wave form of these various voltages.)

Electromyography enables one, by recognition of fibrillation and nascent and normal action potentials, to differentiate accurately denervated, neurotized and normal voluntary muscle.

DISCUSSION

DR. R. P. MACKAY: In clinical neurology, fibrillary twitches are generally considered to indicate disease of the anterior horn cells. This report is interesting in that fibrillations occurred after section of the nerve; the anterior horn would seem to be eliminated as the source.

Were any of these animals curarized? If so, were the fibrillations abolished? Observation on this point would serve to indicate the site of origin of the stimulus to the twitch.

DR. L. J. POLLOCK: With regard to the clinical observation of fibrillation and its relation to the anterior horn, one might say it is unfortunate that the term fibrillation is used to describe what is seen when a nerve is severed as well as what is seen with lesions of the anterior horn. This fibrillation cannot be noted with ordinary light, but is seen with reflected light, usually under magnification. Fibrillation potentials are of the order of about 30 microvolts, whereas in the case of the ordinary motor unit they were expressed in millivolts. What one sees in anterior horn disease is fasciculation. Fibrillation is also seen in anterior horn cell disease when the muscle becomes denervated. Curare has an effect on motor potential as well as on fasciculation. The rate of growth of the axon was studied in muscle by means of indication that a nerve fiber has arrived at the muscle, a high galvanic tetanus ratio being used as an indicator. Where maturation occurs is unknown. Some may consider that restoration of function depends on maturation of the physical structure of the nerve, and others, that it depends on maturation of the myoneural junction; but it takes a long time after a nerve reaches muscle, sometimes one hundred and fifty days, before voluntary motor function returns. If one uses the motor unit potentials as an index, maturation is a far slower process than the growth of the axon—I think the latter is about 1.5 mm. per day. The discovery by electrodiagnosis that a nerve has grown into the muscle precedes by many days the discovery of conduction of impulses by electromyographic tracings.

DR. JAMES A. FIZZELL: The only question which I wish to answer concerns the type of stimulation required to make the animals contract recently neurotized muscles. No electrical stimulation was used. Passive extension of the foot was tried at each examination after the thirty-third postoperative day, but it was discovered that application of pressure to the neuroma in the thigh was the easiest way to determine what voltages the muscles were capable of developing.

Regular Meeting, Jan. 14, 1947

Tactile, Auditory and Visual Areas in the Cerebellum. DR. RAY S. SNIDER.

Distinct areas in the cerebellar cortex which receive nerve impulses from tactile, auditory and visual receptors were studied.

There are two tactile areas: (1) an ipsilateral area in the anterior lobe–lobulus simplex region and (2) bilateral areas in the paramedian lobule. In both the cat and the monkey the tactile area of the anterior lobe and lobulus simplex shows an anatomic localization in the sense that different zones are related to different parts of the body surface. The hindlimb is represented anteriorly in the lobulus centralis; the forelimb, in the culmen, and the head, posteriorly, in the lobulus simplex. On the other hand, the tactile area in the paramedian lobule of the cat shows no such

anatomic localization, since the forelimb and the hindlimb zones are almost conterminous and a head zone has not been found. In the monkey, however, with a large paramedian lobule, different zones of the body are related to different parts of the lobule. The head and face project to the anterior part of the paramedian lobule; the forelimb projects to the middle part, and the hindlimb, to the posterior part. These tactile responses are not relayed from the cerebral cortex, since they occur in the decerebrate animals.

The auditory area is restricted to the lobulus simplex and the tuber vermis. The responses are not affected by decerebration or altered by section of the fifth nerves. They are abolished by section of the eighth nerves, destruction of the cochlea or removal of the inferior colliculi.

The visual area overlaps the auditory, and usually the two areas are conterminous. The cerebellar responses to photic stimuli are not modified by bilateral section of the fifth and seventh cranial nerves or by removal of the eyelids and the extraocular muscles on both sides.

It is predicated that a tactile area exists in the anterior lobe–lobulus simplex region and a second area in the tonsilla–biventral lobule region of the human cerebellum. The auditory-visual area of the human brain is probably located in the large lobulus simplex.

DISCUSSION

Dr. G. von Bonin: I think the anatomist could have predicated somesthetic impulses to the cerebellum if he had studied the fibers composing the lateral moiety of the posterior roots, which are generally considered exteroceptive. The cerebellum receives impulses entering by these fibers through the nucleus proprius and the ventral spinocerebellar tract.

One should expect the cerebellum to work in unison with the cerebral cortex. The massive corticocerebellar connections to which Dr. Snider alluded suggest that. I am not clear whether the corticocerebellar impulses go to those parts of the cerebellum which Dr. Snider mapped out as the end station for sensory impulses. Could he say a few words about that?

Dr. Victor E. Gonda: Dr. Snider described the tactile stimulus quite satisfactorily. Would he give us the type and technic of the auditory and visual stimuli he has applied?

Dr. Ray S. Snider: I am grateful to Dr. Gonda for his question, for there was not time to go into the technical procedures of stimulation. The auditory stimulus was a click, covering approximately the middle voice range, with no extreme high or low tones. My colleagues and I have thought about the question of pure tones but have not carried out experiments. In general, it is the same type of stimulus as that used by the group at Johns Hopkins for working out the auditory area in the cerebral cortex. For photic stimuli we used a 3 watt neon lamp flashing once per second into the atropine-dilated eye. By using a "cold" light and by working in the absence of ocular muscles, we ruled out the possibility of thermal and proprioceptor end organs causing the evoked response.

As to the pathways involved here, we are reasonably sure that the visual pathway is from the eye to the superior colliculus. From there, there are two possible routes: There is a pathway from the superior colliculus to the pontile nuclei; the other is through the brachium conjunctivum. Both pathways are probably concerned. As to the auditory pathway, the fact that these responses can be eliminated by lesions in the inferior colliculus would indicate that it passes through the inferior colliculus; how it gets there I do not know. The auditory and optic areas lie almost in the pontile projection (i. e., the middle lobe of the cerebellum). What it means in terms of cerebellar function one must guess.

Simulated Epilepsy: Report of a Case. DR. REX D. HAMMOND.

A Negro aged 24 entered the Cook County Psychopathic Hospital on March 1, 1946, where a diagnosis of psychopathic personality was made. The patient frankly admitted having faked epilepsy since 1941, when, for $47, he took lessons from an Italian woman in Georgia, his purpose being to get out of the Army. At Camp Gordon Station Hospital, Ga., his skull was trephined in the right temporal area. At Lawson General Hospital, Ga., he submitted to a pneumoencephalographic and, later, an electroencephalographic examination. All these tests, according to the patient, gave normal results. He eventually succeeded in his attempts, for he was given a discharge from the Army for "military inaptitude," under Section 8.

The patient would induce a "spell" at any time on request. He would press his thumbs vigorously into the left side of his neck, let out a cry, fall heavily to the floor and go into typical tonic and clonic seizures. An increased patellar jerk and a Babinski sign could be demonstrated on the left side during one of his seizures. He stated that he was taught how to do this. His pupils were dilated and fixed during the seizure but would react to light normally after the seizure. At any time, if asked to stop, he would quietly rise and brush off his clothes. On one occasion he was persuaded to have a "spell" without pressing his thumbs into the left side of his neck, and this seizure, although similar in all other respects to previous ones, did not prevent his pupils from contracting to light.

An electroencephalogram, obtained at the Illinois Neuropsychiatric Institute, was entirely normal, and during a seizure no abnormal discharges were elicited from the brain. Pressure on the carotid sinus produced only a few extrasystoles in the cardiac tracing.

The problem seems to be one of accounting for the dilated and fixed pupils maintained during the seizure. This sign may be partly explained by an exaggerated ciliospinal reflex, direct pressure on the superior cervical sympathetic ganglion and/or the addition of an emotional factor, as described by Westphal in 1907 and by Loewenstein in 1920, under the heading of spasmus mobilis pupillae.

This patient displayed a remarkable mastery of his body in feigning a convulsive state and in controlling the pupils. His case is one of simulated epilepsy which mimicks true grand mal epilepsy in all respects except the electroencephalographic changes. (A three minute moving picture of the patient's seizures was presented.)

DISCUSSION

DR. ERNEST HASSE: Will Dr. Hammond tell us more about the mental state of the patient? Does he merely produce a wilful act, or does he work himself up into an emotional fit?

DR. HERMAN JOSEPHY: It has been an accepted dogma that elicitation of a Babinski reflex during a seizure is definite proof of true epilepsy. Apparently, modern "teachers of epilepsy" have become cognizant of this concept and are able to teach the reflex to gifted "pupils." However, an experienced observer will never rely on a single sign in his decision. The general pattern of the questionable fit, or one or another detail, may arouse suspicion, and an electroencephalogram will probably quickly settle the problem.

DR. VICTOR E. GONDA: During World War I the symptoms of the war neuroses were mostly somatic manifestations. During World War II changes were chiefly in the psychic sphere. It is dangerous to classify a convulsive seizure as "simulated" in which the pupils do not react to light, no matter how bizarre the seizure might be. It is true that in the moving picture we could not see the

tonic and clonic phases as we are accustomed to see them in so-called idiopathic epilepsy. The convulsive movements were mostly unilateral and almost exclusively tonic. Salivation was unusually heavy. We were told that this man could easily be awakened from his spell. We heard that he took lessons in which he was taught how to simulate fits. Finally, it was stated that his electroencephalographic tracings did not reveal seizure discharges. We were assured that this man was constitutionally psychopathic.

There is no question that there are people who simulate epilepsy. Still, in this case I am not completely convinced that the patient's spells were only simulated. I should like to remind you that a man simulating seizures might still have genuine ones and that normal electroencephalographic tracings do not exclude the possibility of idiopathic epilepsy.

DR. RALPH HAMILL: With regard to the payment of $47, he learned this trick in forty-seven consecutive lessons. However, the fits I saw him have were bilateral.

DR. IRVING C. SHERMAN: Has any one in this audience seen electroencephalographic tracings taken during a genuine convulsive seizure? Are they ever perfectly normal during an attack?

DR. RICHARD B. RICHTER: If I may be permitted to undermine further the confidence of members of the society in the Babinski sign, I should like to recount an experience with a young patient who recently came under my observation. She entered the hospital with a history and signs highly suggestive of a tumor of the third ventricle. However, a pneumoencephalogram was normal, and in the course of time a great deal of emotional disorder was uncovered; so it was finally decided that her symptoms had been hysterical. A disturbing feature was that for some days the patient had shown a Babinski sign on one side. It then came to my attention that she was a faithful reader of *Life* and that shortly before the time of her admission to the hospital this publication had carried an article in which the Babinski sign was illustrated and discussed. I was never able to obtain an admission from the patient that this was where she got her idea, but I strongly suspect that it was so.

DR. REX D. HAMMOND: There was little emotional response in this patient and no particular preparation for the act. We would ask him, "How about a convulsion"; and if he felt like complying he would press on his neck and fall to the floor.

I have not much to add, except that the seizure during which the electroencephalogram was taken was an adequate one. He went through all the motions shown on the screen, and the tracing showed no abnormal brain waves.

The Central Effect of Curare. DR. THEODORE J. CASE and DR. WILLIAM H. FUNDERBURK.

Electroencephalograms were taken on 20 cats after the administration of curare ("intocostrin"). There were no changes in the wave form of the electroencephalogram which were attributable to the use of the drug.

Five cats were conditioned while paralyzed with curare. Any subsequent injection of the drug caused the return of the conditioned response. The response was never elicited when the animal was sufficiently recovered from the drug to be able to stand. Curare inhibits the normally conditioned response even during the period of recovery, at which time muscular twitches are possible. Physostigmine causes the return of the conditioned response in animals conditioned under curare. Beta-erythroidine failed to cause the return of the curare-conditioned response.

The results of this work with curare, beta-erythroidine and physostigmine, as well as the chemical evidence of other investigators, suggests that acetylcholine is involved in the mechanism of the central effect of curare. We have seen that an animal reacts in two ways to identical stimuli, depending apparently on the concentration of acetylcholine in the brain. The suggestion is that when the concentration of acetylcholine is increased the cortex becomes depressed to such an extent that it is no longer functional and the lower centers take over the control of the organism.

DISCUSSION

DR. THEODORE J. CASE: My part in this work has been largely advisory, and I am afraid much of the advice may not have been useful. We have seen fast activity in many animals and have regarded it as normal for these conditions. Whether it is the same as that which has been mentioned by Dr. McCulloch in his studies, I am uncertain. We have not done as much work as he has. The difficulty of telling whether an animal is conscious or not is always great; there is no way of knowing, since he is unable to respond. The fast waves described by Dr. McCulloch may well be evidence of consciousness.

Book Reviews

Textbook of the Nervous System. By H. Chandler Elliott. Price, $8. Pp. 384. Philadelphia: J. B. Lippincott Company, 1947.

This is a unique and interesting book. It discusses the form and function of the nervous system in a manner palatable to the beginner. If this were merely to make an intrinsically difficult subject seem easy, it would not be admirable. But some teachers of cerebral anatomy know (and all should know) that most students are confused and lost in the new subject for want of a basic conception on which to build. Elliott meets this problem in a new way. Penfield, in his introduction to the book, says:

"This textbook is so constructed that the completely uninitiated student can read its opening chapters without bewilderment and master its final descriptions without confusion. The ground is covered twice. In Part One, the descriptions are brief and simple so that the beginner may gain an integrated conception of the whole subject with a minimum of detail. In Part Two this conception is fully elaborated."

Part One, "The Nervous System in Outline," comprises 98 pages and 67 good diagrammatic illustrations. Part Two, 'The Nervous System in Detail," is a good summary of functional anatomy, in 207 pages with 97 illustrations, mostly diagrams that really illustrate. A few, like those on the hypothalamus (fig. 147), are perhaps a little too complex. The chapter on the cerebellum is especially clear. The discussion of the pyramidal system (pages 241 to 245) is a remarkably good exposition of a controversial subject. One may not agree with the author's calling the function of area 6 "psychomotor" or care for the perpetuation of the ancient term "lower motor neurons." Perhaps the following simplification is too diagrammatic:

"In short, as area 4 seems concerned with separate discriminative movements, and area 6 with sequences of activity, the premotor cortex may be said to carry the process farther, to the planning of conduct in relation to the subject's total outlook. In fact, a subject lacking both prefrontal areas is distinctly ape-like in his mental processes."

Examples from clinical experience are used to add meaning and are usually good. When the author says that "frontal leukotomy" is the "surgical treatment for anxiety neurosis," he is not accurate in his psychiatric terms, as he should have said "agitated psychoses" (pages 206 and 245). I like his use of the term "frontal leukotomy"; neither "prefrontal" nor "lobotomy" is a word that can be upheld.

Pages 329 to 367 contain a short atlas of the cord and brain, in 25 plates. They are good photographs with diagrammatic keys.

A good book, this is, and a boon to the beginner!

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CONTENTS